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# Clinical characteristics and management of growth hormone excess in patients with McCune-Albright syndrome

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## Abstract

**Objective:** McCune-Albright syndrome (MAS) is a sporadic, postzygotic disease presenting with fibrous dysplasia, cafe-au-lait spots and multiple endocrinopathies. Growth hormone (GH) excess is an uncommon but potentially severe complication of MAS. This study aims to describe the clinical manifestations of GH excess in the context of MAS, and analyze the responses of these patients to treatments.

**Design: Retrospective clinical study.**

**Methods:** Clinical data from 52 MAS patients were analyzed. Serum GH and IGF1 levels, as well as nadir GH levels after an Oral Glucose Tolerance Test and alkaline phosphatase (ALP) levels were determined before and after the treatment.

**Results: In total,** 13 MAS patients (25%) had the complication of GH excess, including 10 males (76.9%). Among them, all had FD, and 6 patients had sphenoidal bone involvement. Visual deficits were present in 8 patients, and hearing deficits were present in 5. Olfactory dysfunction was observed in 3 patients. Evident pituitary adenomas were confirmed in 9 patients by MRI. These patients underwent surgery with or without pretreatment of long-acting somatostatin analogue octreotide, and 6 achieved complete remission. The serum ALP levels decreased significantly after treatment for GH excess.

**Conclusions:** MAS with GH excess is more common in male patients. GH excess can lead to more severe skeletal lesions in MAS patients that involve more of the craniofacial bones. Complete trans-sphenoidal complete tumor excision with neuronavigational guidance is effective and could lower ALP levels. LAR is

recommended as a preoperative treatment and when patients fail to achieve complete remission after surgery.

**Keywords：** McCune-Albright syndrome, growth hormone excess, pituitary adenoma, trans-sphenoidal tumor excision

## Introduction

McCune-Albright syndrome (MAS, OMIM 174800) is a sporadic, postzygotic disease with an estimated prevalence of between 1/100,000 and 1/1,000,000[1]. It was first described as a clinical triad of polyostotic/monoostotic fibrous dysplasia (FD), cafe´-au-lait pigmented skin lesions, and precocious puberty by McCune[2] and separately by Albright[3] in the 1930s. Other endocrinopathies in the context of MAS were subsequently identified, including hyperthyroidism[4], hypercortisolism[5], pituitary adenomas secreting growth hormone (GH) and/or prolactin (PRL) [6, 7], and hypophosphatemic osteomalacia[8]. GH excess, which is present in 10%-20%[9] of MAS cases, is a serious endocrine complication associated with craniofacial morbidities, including visual and hearing deficits, as well as cardiovascular disease and metabolic syndrome. However, the treatment of GH excess in MAS patients remains challenging. Neurosurgical excision is often difficult due to severe fibrous dysplasia at the base of the skull[10], and radiotherapy (RT) may precipitate bone sarcomatous transformation[11]. To date, several cases have been reported involving treatment for GH excess in MAS, but only a few achieved satisfactory outcomes. The aim of this study is to describe the clinical manifestations, treatment, and outcomes of patients with MAS patients complicated by GH excess.

## Subjects and Methods

### Patients

All of the studies were performed according to the rules of the hospital medical ethics

committee. Informed consent was obtained in accordance with the institutional guidelines.

Clinical data from 52 MAS patients at Peking Union Medical College Hospital from November 1991 to April 2016 were retrospectively analyzed, and those with the complication of GH excess were followed up.

**Diagnosis of MAS and GH excess**

A diagnosis of MAS was made when at least two of the following cardinal features were present: café-au-lait skin pigmentation, polyostotic/monostotic bone fibrous dysplasia (FD) and hyperfunctioning endocrinopathies. Technetium whole body bone scanning, CT scans and X-ray imaging were used to confirm bone lesions. The serum alkaline phosphatase (ALP) levels were assessed. Visual, hearing and olfactory functions were evaluated by the otolaryngology and ophthalmology consultation group. A T&T Olfactometer was used for Standardized Olfactory Test. Endocrine hormone levels were assessed to identify endocrinopathies associated with MAS.

The diagnosis of GH excess was based on clinical symptoms and confirmed by high levels of GH (IMMULITE 2000 GH analyzer, Siemens Healthcare Diagnostic Inc.), age- and sex-adjusted insulin-like growth factor1 levels (IGF1, IMMULITE 2000 IGF1 analyzer, Siemens Healthcare Diagnostic Inc.), and nadir GH levels after an oral glucose tolerance test (OGTT) with GH levels that were greater than 1.0 ng/ml. The

nadir GH levels of each patient were recorded at baseline and after surgery. The IGF1 Z-scores were adjusted for age and gender according to the normal values of serum IGF1 (the $5^{th}$ and $95^{th}$ percentiles), and Z-scores greater than 2.0 were considered elevated.

Pituitary magnetic resonance imaging (MRI) was used to identify compression associated with pituitary tumors. All of the patients underwent blood pressure testing, thyroid ultrasound, echocardiograms and OGTT, and co-morbidities including diabetes mellitus, hypertension and heart disease were noted.

**Pathological Analysis**

Pituitary adenoma tissues were surgically removed, fixed in 10% formaldehyde, embedded in paraffin, and cut into 3-μm-thick sections for immunohistochemical staining. Immunohistochemistry was performed using the avidin-biotin-peroxidase method. The sections were incubated with the following antisera: anti-GH, anti-PRL, anti-adrenocorticotropic hormone (Dako, Carpinteria, CA, USA; A0570, A0569, A0571), anti-thyroid-stimulating hormone, anti-follicle-stimulating hormone, and anti-luteinizing hormone (Long Island Biotec. Co., Ltd, Shanghai, China; M-0497, M-0255, M-0368).

**Treatment**

Nine patients underwent navigation-assisted transsphenoidal pituitary tumor

resectioning. The serum levels of IGF1, PRL and ALP, as well as nadir GH levels after OGTT, were evaluated after treatment and during follow-up.

Remission of acromegaly was assessed based on the normalization of GH/IGF1 levels. The criteria for disease control were a normal IGF1 level for age and gender (Z score<2.0) and an OGTT-suppressed GH level of no more than 1.0 ng/mL.

The literature regarding treatments for MAS patients with GH excess from 2001 to 2015 was reviewed, and the patients who underwent transsphenoid surgery was noted.

**Statistics Analysis**

Descriptive statistics were used to characterize the demographic and laboratory data. The IGF1 Z-scores were calculated according to an equation described in Ref [12]. The height and ALP level Z-scores were based on reported distributions of height/ALP levels in Chinese population[13-15]. T-tests were performed to make comparisons between MAS patients with GH excess and MAS patients without GH excess, as well as between GH patients before and after surgery. A $P<0.05$ was regarded as statistically significant. The analyses were performed using SPSS 15.0 and GraphPad Prism Version 6 (GraphPad Software Inc., San Diego, CA).

# Results

**Clinical Characteristics**

Thirteen patients (25%) with GH excess were identified among 52 MAS patients (mean age at diagnosis of MAS: 27.5±13.4 yr.), including ten males (76.9%) and three females. The onset of MAS symptoms occurred at 3.3±6.2 years of age, and the mean age of diagnosis of GH excess was 24.2±11.2 years. The principal clinical characteristics, endocrine abnormalities and MRI features are listed in Table 1. All of the patients presented with FD. Craniofacial bones were involved in all cases, and the sphenoidal bone was involved in 46.1% of cases. Appendicular bones and axial bones were both involved in 46.1% of the patients. Six of the patients who had surgery (patient 2,3,7,8,10, and 11) had FD affecting the sphenoid. Visual field deficits occurred in eight patients (owing to optic canal stenosis in six), FD-related hearing deficits were observed in five, and olfactory dysfunction was present in three. The ALP z-scores of the MAS patients with GH excess were higher than those without GH excess (Fig. 1B), and all except one patient had cafe´-au-lait pigmented skin. Peripheral precocious puberty was observed in patients 2 and 12. Pituitary adenomas were confirmed by MRI in nine patients(69.2%), seven of which were macroadenomas (maximum diameter>1.0 cm) and two of which were microadenoma (maximum diameter≤1.0 cm). Six patients had the complication of PRL hypersecretion. Thyroid involvement was observed in four patients, including primary hyperthyroidism in two patients and abnormalities of the thyroid gland based on ultrasound without frank hyperthyroidism in two patients (total: 30.8%). Acromegalic cardiopathies were observed in three patients, including left ventricular hypertrophy (LVH), atrial or aortic enlargement, and pericardial effusion. Four patients had

impaired glucose tolerance (IGT), and two patients were hypertensive.

Thirty-nine of the MAS patients did not have the complication of GH excess (mean age at diagnosis of MAS, 13.8±9.6 years), and 28.2% of these patients were male. There were no significant differences in age of diagnosis between the patients with and without GH excess. FD occurred in 76.9% of the MAS patients without GH excess. Among them, only three patients were diagnosed with conductive hearing loss and two with visual deficits due to a narrowing of the auditory/optic canals, while none presented with hyposmia. Of the 22 cases with complete records, craniofacial bones were involved in 81.2% of the cases, and the sphenoidal bone was involved in only 15.4%. Appendicular bones and axial bones were involved in 87.5% and 56.2% of the cases, respectively. Twenty-three patients (59.0%) underwent precocious puberty (PP). Two of the patients had primary hyperthyroidism, and three had thyroid nodules without abnormal thyroid function (total: 22.7%).

**Treatment Outcome**

Four of the patients without definitive radiographic evidence of pituitary adenomas did not undergo surgery, and the GH excess was not controlled at the time of discharge. The remaining nine patients underwent navigation-assisted transsphenoidal pituitary tumor resection. The pathology showed negative margins, and the immunohistochemical analysis confirmed pure GH (n = 3), mixed GH-PRL (n = 5) and mixed GH-PRL-LH (n=1) adenomas. One of the nine patients had received

gamma knife treatment for his tumor at another hospital prior to the surgery, and his symptoms of GH excess reoccurred. Notably, he developed osteosarcoma at the pterygopalatine fossa during the postoperative follow-up. Two of the patients had been injected with 20 mg of the long-acting somatostatin analogue octreotide (LAR) (Sandostatin LAR, Novartis) once a month for 3-4 months before the surgery. However, no significant tumor shrinkage was observed by MRI. One patient had taken LAR and then bromocriptine for 10 years before he underwent the surgery, but the GH excess was not controlled. One patient was treated with surgery followed by LAR.

The follow-up time ranged from 0.3 to 9.6 years. Total tumor excision was achieved in all of the patients, as confirmed by postsurgical MRI. No additional pituitary deficiencies were found post-surgically. Six patients achieved complete remission, with a reduction in GH/IGH-1 to normal levels. Meanwhile, three patients partially responded, and their GH levels were controlled by LAR postoperatively (Table 2). The serum ALP z-scores decreased significantly after remission of GH excess (~26.3%, $p<0.001$)(Fig. 1A).

Previous reports of treatments for GH excess in MAS patients and their outcomes are summarized in Table 3. Of the patients who underwent navigated transsphenoidal surgery without preoperative medication or with ineffective medication, 2 out of 7 achieved complete remission after surgical excision alone or followed by

post-operative medication/radiotherapy, and 5 out 7 patients partially responded to the treatment.

## Discussion

MAS is caused by a postzygotic-acting mutation in the *GNAS1* gene encoding the alpha chain of the heterotrimeric G protein (Gsa) that is involved in stimulating the adenyl cyclase-cAMP pathway [16, 17]. However, the pathophysiology of GH excess in MAS at the cellular and organ level is not clearly understood. The results of this study shows that 26.4% of MAS patients had the complication of GH excess, which is in accordance with previous reports[6, 7, 18].

GH excess in the context of MAS has its own characteristics. In this study, we found that the MAS patients with GH excess were diagnosed at younger ages (mean age of onset, 24.2 years) than patients with classical acromegaly/gigantism (mean age of diagnosis, 48.7 years) [19], which is consistent with previous reports[20]. Furthermore, 76.9% of male MAS patients suffered from GH excess, whereas the percentage of males with classic acromegaly/gigantism has been reported to be lower (52.8%) [19]. GH excess is associated with growth acceleration and/or facial dysmorphism. However, growth acceleration may be obscured in MAS patients with PP, and facial dysmorphism is often difficult to assess due to craniofacial FD. Of the eight patients with an adolescent onset of GH excess in this study, four presented with accelerated growth, and three of these patients exhibited PP. Enlarged feet and hands offer

important clues for acromegaly. Co-secretion of PRL was observed in 46.1% (6/13) of MAS patients with GH excess, which is in accordance with the consensus that the prevalence of hyperprolactinemia is higher in patients with MAS than in those with classical acromegaly (71-92% vs. 30-40%)[7, 12, 21].

In addition, there are several important differences between MAS with GH excess and MAS without GH excess. A greater proportion of the GH excess patients were male, and GH excess may aggravate the skeletal lesions associated with MAS. In this study, FD was presented in 76.9% of the MAS patients without GH excess compared with 100% of the patients with GH excess. Despite the fact that craniofacial bones were commonly involved in both cases, FD affecting the sphenoid bone was observed more often in patients with GH excess (46.1%) compared to those without (15.4%). In addition, the involvement of the appendicular and axial bones was less commonly observed in patients with GH excess. Therefore, we should prescribe systematic hormone tests and pituitary contrast-enhanced MRIs for MAS patients with confirmed sphenoidal bone damage or the absence of extracranial bone involvement to rule out GH excess and pituitary adenomas. Higher concentrations of GH accelerate craniofacial FD and increase the risk of olfactory, hearing and vision loss [12]. We found that hyposmia, sensorineural hearing loss and visual deficits were less common in the MAS patients without GH excess (with vs. without GH excess: 38.4% vs. 12.8%). Although the mass occupying effects of the GH macroadenomas could in part explain the visual deficits, the visual problems were more frequently related to a

narrowing of the optic canal (75%), which is consistent with previous reports[20]. Bone turnover is increased in acromegaly patients who have significantly higher levels of markers of both bone formation and resorption[22]. These biomarkers including ALP often correlate with the extent and severity of skeletal involvement in MAS[23]. As shown in the result section, serum ALP levels decreased significantly when the GH excess was controlled, indicating that treatment for GH excess may improve FD. There were significant differences in the ALP levels between MAS patients with GH excess and MAS patients without GH excess (Fig. 1), and further studies are warranted regarding the relationship between GH and skeletal lesions. Moreover, GH excess is associated with glucose intolerance, hypertension and acromegalic cardiomyopathy, which might increase the morbidity and mortality[24].

Three of the patients did not exhibit any symptoms of GH excess during thorough examinations after the diagnosis of MAS. However, hormone tests revealed elevated GH levels, and an MRI confirmed the presence of a pituitary adenoma in one of them. Therefore, systematic hormone testing and pituitary contrast-enhanced MRI may be beneficial for MAS patients. Previous reports have indicated that pituitary adenomas tend to be absent or smaller in MAS patients with GH excess[25], and widespread and diffuse pituitary gland disease has been identified even in patients who appeared to have discrete adenomas on MRI[26]. However, pituitary adenomas were confirmed pathologically in 69.2% of the patients in this study, and seven were macroadenomas. This is probably a consequence of the development of imaging techniques, as well as

biases due to the small sample sizes and single-center studies.

Current treatments for GH excess in MAS include radiotherapy, surgery and medication (somatostatin receptor ligands, the dopamine agonist Cabergoline, and the GH receptor antagonist Pegvisomant). Although a review published in 2014 suggested that surgical excision might not be beneficial for MAS patients with pituitary adenomas because skeletal lesions usually makes the operation more challenging[20], considerable technical progress has been made in the past few years, so we propose that transsphenoidal excision with neuronavigational guidance might be a good choice for treatment. As reviewed in Table 3, 2 out of 7 of the previously published cases of patients who underwent transsphenoidal surgery without preoperative medication or with ineffective medication achieved complete remission after surgical excision alone or when followed by post-operative medication/radiotherapy, and 5 out of 7 patients had a partial response. Moreover, in this study, 6 out of 9 patients who underwent navigation-assisted transsphenoidal pituitary adenomectomy achieved complete remission according to endocrinological criteria. Notably, 4 of the 6 patients had FD affecting the sphenoid. Among the patients who underwent surgery alone, the complete remission rate was 75% (3/4), which is consistent with the reported rate for classic acromegaly patients (74%)[27]. Individual differences among patients, improvements in neurosurgical techniques and the experience of the surgeons may explain different remission rates.

Treatment with medication is also of vast value. Among the cases reviewed in the literature, 46 patients took medication alone, including octreotide, LAR, cabergoline (CAB, a dopamine agonist), pegvisomant (a GH receptor antagonist), and a combination of above. The symptoms of 22 patients were completely alleviated by LAR treatment alone or when combined with other drugs. LAR, as the first-line drug for GH excess, was able to normalize IGF1 levels in approximately 50% of the patients and result in a partial response in the rest. The ability of pegvisomant to normalize IGF1 levels is similar to LAR, but it is not as effective at treating other GH excess-related symptoms such as fatigue and sweating[28]. Patients frequently exhibit inadequate responses to CAB, and the administration of medication before and after surgery is favorable for complete relief. Considering the potential for tumor shrinkage and the down-regulation of GH/IGF1 levels by somatostatin analogues, preoperative treatment of acromegaly patients with these drugs reduces comorbidity and facilitates adenoma removal[27, 29]. Two of the patients in this study received preoperative LAR. However, no tumor shrinkage was observed. Therefore, well-designed studies are required to further assess the role of preoperative therapy.

Radiotherapy is considered as the last choice due to the risk of bone sarcomatous transformation. MAS has been shown to be associated with the malignant transformation of FD, as well as malignancies of thyroid and breast[30]. Liu et al[31] reported a case involving a MAS patient who was treated with radiation therapy and later developed undifferentiated chondrosarcoma of the malignant fibrous

histiocytoma subtype in the sellar region afterwards. In this study, it is highly suspected that the osteosarcoma of the pterygopalatine fossa that patient 8 developed was related to the radiotherapy. We suggest that radiotherapy be used only when surgery is not possible and medication fails.

It should be noted that this study was limited by the inherent drawbacks of retrospective analyses. Small sample sizes were also a major problem due to the low incidence rate of MAS. These issues could be partially resolved by delicate statistical analysis and a supportive literature reviewed. Another limitation was the lack of IGF1 data for patient 5 as the GH nadir of this patient was just below the cutoff of 1ng/mL. In addition, ALP levels were the only biomarker for skeletal lesions analyzed, so further exploration is warranted.

## Conclusion

MAS with GH excess is more common in male patients, and GH excess could lead to more severe skeletal lesions and more involvement of the craniofacial bones. Complete trans-sphenoidal tumor excision with neuronavigational guidance is effective and could lower ALP levels, and LAR is recommended as both a preoperative treatment and for when patients fail to achieve complete remission after surgery.

## Declarations of interest

There is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

## Funding

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Table 1. Clinical characteristics of the 13 MAS patients with the complication of GH excess

| Case No. | Sex | Age at diagnosis of MAS | Age at diagnosis of GH excess | Height Z-score | FD | SD | PP | Hearing or olfactory deficits | VD | Hyper-endocrinism | Pituitary tumor (MRI) | GH excess-related complications |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| **1** | M | 42 | 42 | 1.38 | P | + | - | - | - | GHH | suspected diagnosis | shin-soft tissue infection of the submaxillary |
| **2** | F | 6 | 6 | 7.38 | P | + | + | - | Bilateral* | GHH, PH | macro | - |
| **3** | M | 19 | 19 | 2.05 | P | + | - | external auditory canal atresia | unilateral | GHH, PH | macro | LVH |
| **4** | M | 36 | 36 | 1.72 | M | + | - | conductive deafness | unilateral | GHH | macro | HTN, aorta broadening, pericardial effusion, IGT |
| **5** | F | 27 | 27 | 0.55 | P | + | - | conductive hearing loss, hyposmia | bilateral | GHH, PH | macro | IGT |
| **6** | M | 25 | 25 | -0.45 | P | + | - | conductive | bilateral | GHH, PH,HT | pituitary | left atrial enlargement, IGT |

| | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | deafness | | | enlargement | |
| **7** | F | 12 | 12 | 2.4 | P | + | - | hyposmia | bilateral | GHH | micro | - |
| **8** | M | 35 | 33 | 1.72 | M | - | - | hyposmia | unilateral | GHH, PH | macro | - |
| **9** | M | 46 | 46 | 3.05 | P | + | + | - | - | GHH | micro | HTN, DM |
| **10** | M | 43 | 26 | 2.72 | P | + | | - | - | GHH, PH | macro | - |
| **11** | M | 47 | 46 | 0.05 | P | + | | - | unilateral | GHH | macro | - |
| **12** | M | 9 | 9 | 1.43 | P | + | + | - | - | GHH | N/A | - |
| **13** | M | 22 | 22 | 2.05 | P | + | | tinnitus | - | GHH, HT | N/A | - |

FD : fibrous dysplasia; SD: skin dysplasia (café-au-lait skin pigments); PP: precocious puberty; VD: visual deficit (*: VD related to pituitary adenoma, others refer to FD-related VD); HT: hyperthyroidism; GHH: growth hormone hypersecretion; PH: prolactin hypersecretion; LVH: left ventricular hypertrophy; HTN: hypertension; IGT: impaired glucose tolerance; DM: Diabetes Mellitus

+: positivity; -: negativity; P: poly; M: mono

Table 2. The hormonal changes, treatments, tumor pathologies and outcomes of MAS patients with GH excess that underwent surgery.

| | Pre-treatment | | | | | | | Post-treatment | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | IGF1* | nadir | | | | | Tumor size | Follow-up | IGF1 | nadir | | | |
| Case | (ng/mL) | Z score | GH | PRL | Treatment | IHC positivity | (cm) | time (years) | (ng/mL) | Z score | GH | PRL | Outcomes |
| **2** | 954 | 11.1 | 35.3 | 204.4 | Surgery + LAR | GH, PRL | N/A | 7.8 | 448 | 4.4 | 4.3 | 41.7 | PR |
| **3** | 868 | 5.8 | 34.7 | 41.0 | Surgery | GH, PRL | 2.0×2.0 # | 5.6 | 147 | -1.1 | 0.3 | 2.4 | CR |
| **4** | 863 | 12.9 | 62.7 | 7.4 | LAR + Surgery | GH | 1.7×1.2×1.0 | 5.0 | 137 | -0.7 | 0.2 | N/D | CR |
| **5** | 804 | 9.4 | 20.0 | 52.8 | Surgery | GH, PRL | 2.0×1.5×1.2 | N/A | N/A | N/A | 0.95 | 5.5 | CR |
| **7** | 1593 | 7.6 | 8.2 | 15.9 | LAR + Surgery | GH | 1.2×0.9 # | 8.1 | 48 | -1.6 | 0.06 | N/D | CR |
| **8** | 1252 | 18.2 | 12.5 | 57.8 | γRT[a] + Surgery | GH, PRL | 2.0×0.9×1.1 | 9.6 | 138 | -0.9 | 0.44 | 3.08 | CR |
| **9** | 947 | 16.5 | N/A | 2.9 | LAR+bromocryptine +Surgery | GH, PRL, LH | 1.0×0.8×0.7 | 0.6 | 676 | 10.9 | 2.38 | 2.73 | PR |
| **10** | 560 | 8.4 | 10.4 | 43.4 | Surgery | GH, PRL | N/A | 5.4 | 789 | 12.4 | 4.17 | 15.2 | PR |
| **11** | 601 | 9.3 | 6.14 | 7.75 | Surgery | GH | 1.41×0.94# | 0.3 | 207 | 1.1 | N/A | N/D | CR |

∗Normal values of serum IGF1 (the 5th and 95th percentiles): Case 2 (6 yrs.): 52–297; Case 3 (19 yrs.): 141–483; Case 4, (36 yrs.): 109-284; Case 5(27 yrs.): 117-329; Case 7(12 yrs.): 143-693, Case 8 (35 yrs.): 115-307; Case 9&11(46, 47yrs.): 94-252; Case 10(43yrs.): 101-267;

#data of the third dimension was missing;

nadir GH: the lowest values of GH suppressed by OGTT;

LAR: long-acting somatostatin analogue octreotide

γRT = gamma knife radiotherapy; a: operated in other hospital;

N/D, not done; N/A, not available;

CR: complete remission; PR: partial response

Table 3 Treatments for GH excess in MAS patients and their outcomes: a review of literature from 2001 to 2015

| Year | Area | No. of cases | Sex/Age (yrs) | Treatment for GH excess | Outcome | Ref. |
|---|---|---|---|---|---|---|
| 2001 | Germany | 1 | M/8[a] | LAR | PR | 32 |
| 2002 | NIH, USA | 10 | M:F,2:8/ Range:4-40 | CAB (n=7) | 6/7 PR | 12 |
| | | | | LAR (n=8) | 4/8 effective | |
| | | | | CAB and LAR (n=4) | 4/4 PR | |
| 2003 | India | 3 | M/28[a] | transfrontal pituitary adenomectomy+ RT in all three | no response | 33 |
| | | | M/25[a] | | PR | |
| | | | M/19[a] | | PR | |
| 2005 | Australia | 1 | M/8.5 | octreotide+LAR | PR | 34 |
| 2006 | Turkey | 1 | M/52 | LAR | PR | 35 |
| 2006 | Greece | 6 | M/9 | LAR | CR | 36 |
| 2006 | NIH, USA | 5 | M/33 | LAR+CAB and pegvisomant | Not normalized IGF1 | 28 |
| | | | F/39 | LAR +pegvisomant | Normalized IGF1 | |
| | | | M/17 | LAR+ pegvisomant | Normalized IGF1 | |
| | | | F/37 | LAR+CAB and pegvisomant | Normalized IGF1 Increased tumor size | |
| | | | F/13 | LAR+CAB and pegvisomant | Normalized IGF1 | |
| 2007 | Korea | 1 | M/23 | LAR and bromocriptine | Normalized PRL GH/IGF1 decline | 37 |

| | | | | | | |
|---|---|---|---|---|---|---|
| 2008 | Japan | 1 | M/15 | Transfrontal partial adenomectomy+octreotide+ neurological decompression of the optic nerve+LAR and CAB | CR | [38] |
| 2009 | Brazil | 1 | M/29[a] | LAR+CAB | CR | [39] |
| 2010 | Poland | 1 | F/41 | LAR | No response | [40] |
| 2011 | Japan | 1 | M/39[b] | adenomectomy+cyberknife RT | normalized GH and ACTH | [41] |
| 2011 | USA | 2 | F/21[a] | ① surgery(TSA)+ short-acting octreotide ②LAR+ second resection due to residual/recurrent pituitary microadenoma+ lanreotide | residual tumor NCR | [10] |
| | | | F/29 | LAR | PR | |
| 2012 | NIH,USA | 3 | M/19 | selective removal(TSA) | PR | [26] |
| | | | F/29 | selective adenomectomy (TSA) | PR | |
| | | | M/19 | total hypophysectomy(TSA) | CR | |
| 2012 | India | 1 | M/33 | subtotal excision(TSA)+ CAB | PR | [42] |
| 2013 | NIH | 26 | M:F 6:7 | LAR(n=11) | Effective | [43] |
| | | | | LAR + LAR and Pegvisomant(n=5) | 4/5 effective | |
| | | | | LAR + Pegvisomant(n=1) | IGF-I decline but not normalized | |
| | | | | LAR + Surgery(TSA) (n=2) | 1/2 effective | |
| 2014 | France | 3 | F/22 | LAR | PR | |

| | | |
|---|---|---|
| M/35 | LAR + Pegvisomant | CR |
| F/64 | LAR + LAR and DA +γ-nife radiotherapy+ Pegvisomant | CR |

surgery: transsphenoidal pituitary tumor resection;

a: complicated by PRL hypersecretion; b: complicated by hypercortisolism;

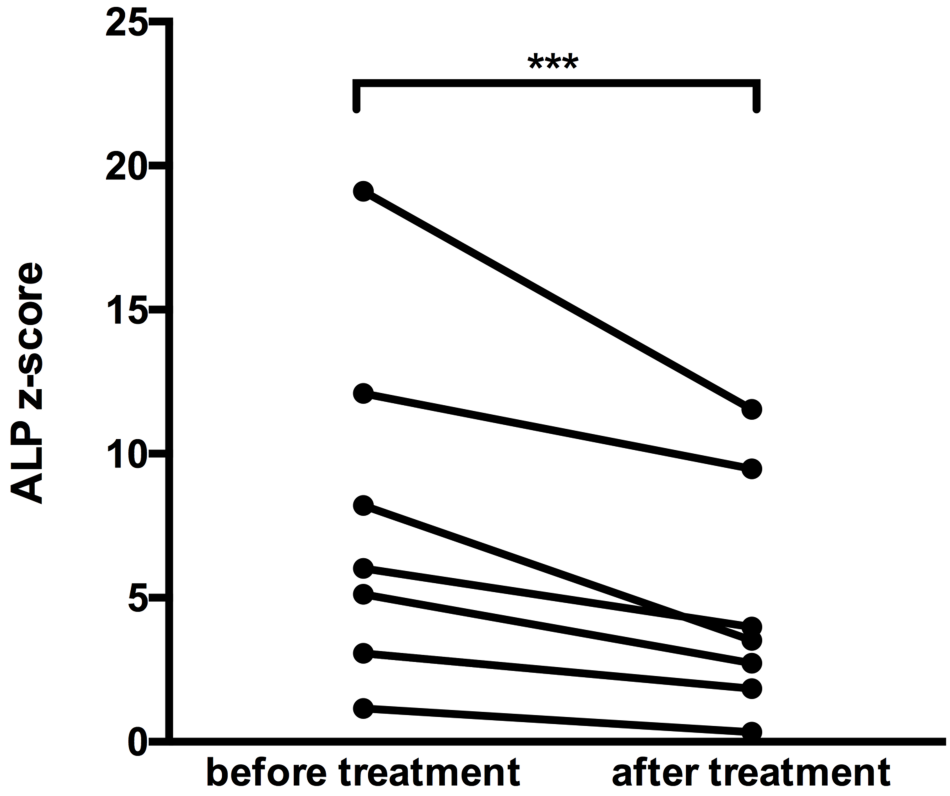
CAB: cabergoline; LAR: long-acting somatostatin analogue octreotide; DA: dopamine antagonist

TSA: Transspheinoidal approach

CR: complete remission; NCR: not complete remission; PR: partial response

+: followed by

A




B