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Title: Growth hormone (GH) - insulin like growth factor 1 (IGF-1) axis hyperactivity on bone fibrous dysplasia in McCune-Albright Syndrome

Short running title: GH hypersecretion in MAS

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Conflict of Interest Statement

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Summary

Context: In fibrous dysplasia (BFD) normal bone and bone marrow are replaced by fibro-osseous tissue, leading to fracture, deformity and pain. BFD may be isolated, or in association with cutaneous hyperpigmentation and/or hyperfunctioning endocrinopathies, termed McCune-Albright syndrome (MAS). GH hypersecretion has been described in 10-20% of MAS-BFD patients. Aim of the study is to determine the impact of GH-insulin like growth factor 1 (IGF1) axis hyperactivity on MAS-BFD morbidities and the efficacy of GH excess therapy.

Design and patients: A multicentric cross-sectional analysis was conducted on three different MAS cohorts. From 195 MAS patients 37 subjects (19%) with GH excess were identified and compared with 34 MAS controls without GH hypersecretion.

Results: Mean head circumference SDS, was significantly higher in GH excess: 4.025 SDS vs 0.683 SDS ($p < 0.0001$). The risk of optic neuropathy (Odds ratio 4.231; $p = 0.039$), hearing deficit (Odds ratio 2.961; $p = 0.0481$), facial asymmetry (Odds ratio 6.563; $p = 0.0192$), malignancies (Odds ratio 15.24; $p = 0.0173$) were higher in GH excess group. Overall, pharmacotherapy (octreotide alone 10-30 mg/month or with pegvisomant 10-20 mg/day) was effective in IGF1 normalization (IGF1 Z-score between -2 and +2 SDS) in 21/29 patients (72.4%) with good compliance to the regimen. Late diagnosis and GH excess treatment after 16 years old of age was associated with an increased

risk of optic neuropathy (Odds ratio 4.500; $p=0.0491$) and growth of pituitary adenomas (Odds ratio 7.846; $p=0.050$).

Conclusions: GH-IGF1 hyperactivity increases risk of morbidities in MAS. Medical therapy is effective in normalizing IGF1 in most patients, and early treatment during paediatric age is associated with a decreased risk of optic neuropathy and GH-secreting adenomas growth.

Introduction

Bone fibrous dysplasia (BFD) is a skeletal disorder in which normal bone and bone marrow are replaced by fibro-osseous tissue, leading to fracture, deformity and pain (1,2). BFD may occur in isolation, or in association with cutaneous hyperpigmentation and/or hyperfunctioning endocrinopathies, termed McCune-Albright syndrome (MAS) (3,4). BFD/MAS arises from activating mutations in the *GNAS* gene, which encodes for the α -subunit of the Gs stimulatory protein ($Gs\alpha$) (5,6). Mutations occur post-zygotically, leading to mosaic disease with wide variability between individuals (7-8). Disease burden is determined by the embryonic stage during which the mutation occurs, and the locations to which mutated progenitors subsequently migrate (9).

In bone, the downstream effects of constitutively elevated $Gs\alpha$ lead to proliferation of undifferentiated bone marrow stromal cells (10,11). Normal bone is replaced with structurally and functionally abnormal matrix, with extensive marrow fibrosis. Endocrinopathies include gonadotropin-independent precocious puberty resulting from recurrent ovarian cysts in girls and autonomous testosterone production in boys; testicular lesions with or without associated gonadotropin-independent precocious puberty; thyroid lesions with or without non-autoimmune hyperthyroidism; growth hormone (GH) excess; FGF23-mediated phosphate wasting with or without hypophosphatemia; and neonatal hypercortisolism (12-13).

Approximately 10%-20% of individuals with BFD/MAS harbour *GNAS* mutations in the anterior pituitary that can lead to autonomous GH secretion, typically accompanied by hyperprolactinemia (14).

GH excess in MAS is reported to be associated with possible vision loss, macrocephaly and increased post-operative regrowth after craniofacial surgery (15,16,17). Thus, in such population we hypothesized an higher risk of craniofacial morbidity and in extension also a systemic role on MAS phenotype.

Medical therapy is the preferred first-line treatment: options include (alone or in combination) octreotide and the growth hormone receptor antagonist pegvisomant (14) whereas surgery and radiotherapy are controversial.

Materials and methods

Aim of the study

The purpose of this study is to establish prevalence of growth hormone (GH) hypersecretion in MAS through the study of three large cohorts; to detect clinical, hormonal and radiological alterations for the diagnosis; to establish prevalence of associated hyperprolactinemia; to determine the impact of GH-insulin like growth factor 1 (IGF1) axis hyperactivity on BFD morbidities and bone turn-over markers and if therapy for GH excess is able to prevent these co-morbidities.

Design and Setting

A retrospective, multicentric cross-sectional analysis was conducted at National Institutes of Health, NIH, NIDCR, Bethesda, USA; at the Department of Pediatric Endocrinology, Regina Margherita Children Hospital, University of Torino, Italy; and at Pediatric Endocrinology and Diabetology; Royal Children's Hospital; Parkville, Australia. Three large cohorts affected by MAS were analyzed: 131 patients (50 males and 81 females) from the American cohort, 34 subjects (10 males and 24 females) from the Italian cohort, and 30 patients from the Australian cohort (18 males and 12 females). All patients were screened based on clinical history, auxological, hormonal and imaging assessment for possible GH excess, morbidities, bone turn-over serum markers, other endocrinopathies and clinical manifestations including pain and presence of neoplasia. Treatment embraced octreotide, pegvisomant, transphenoidal surgery and radiotherapy.

Data collected at baseline

Sex, age, age at MAS diagnosis, height and height SDS at GH hypersecretion detection (pre-therapy), other endocrinopathies, malignancies, craniofacial BFD and long BFD, skull and total BSS (bone scan score), hormonal assessment (GH random, GH OGTT suppression test, frequent overnight GH sampling, IGF1, IGF1 SDS, prolactin), head circumference and head circumference SDS, macrocephaly, treatment for GH hypersecretion, other therapies, bone turn-over serum markers (alkaline phosphatase, osteocalcin), pituitary magnetic resonance imaging (MRI) and craniofacial computed tomography (CT).

Data collected at the end of the follow-up period

Age, height and height SDS, IGF1, IGF1 SDS, prolactin, pituitary MRI, bone turn-over serum markers (alkaline phosphatase, osteocalcin), morbidities (sphenoid sinus opacification, optic neuropathy, hearing deficit, malocclusion, facial asymmetry, cranio-facial pain and pain in other districts), other endocrinopathies and malignancies.

Hormonal analysis

Testing included GH, IGF1, prolactin, GH suppression test, and frequent overnight GH sampling. GH excess diagnosis was made based on two confirmatory tests. GH and IGF1 levels were drawn fasting at 08.00 h on 2 days and averaged GH, IGF1 and prolactin levels were obtained by chemiluminescence immunoassay. For random GH values greater than 5.0 ng/ml were considered consistent with GH excess. For IGF1, values were converted to Z-scores using reference ranges for age and gender. Z-scores greater than 2.0 were considered elevated. GH suppression testing was performed including administration of oral glucose 100 g and measurement of GH levels at 0, 30, 60, 120, and 180 min. Lack of GH suppression below 1 ng/ml at 120 min was considered elevated. Frequent overnight GH sampling involved collecting samples every 20 min from 20.00 to 08.00 h. A lack of nadir below 1.0 ng/ml was considered elevated. Prolactin normal range were considered 2-12 mg/l for males; 4-20 mg/l for females.

At baseline evaluation, MAS patients in the control group showed mean random GH and IGF1 SDS levels in the normal ranges; no additional tests investigating the GH-IGF1 axis were performed in this group.

The subsequent assays were used and standardized across countries: for GH and prolactin Immulite 2000 analyzer Siemens Medical Solutions Diagnostics, Deerfield, IL for American patients; Nichols Institute Diagnostics, San Clemente, CA, USA for Italian patients; Cobas, Roche, Basel Prolactin Vitros and Ortho clinical diagnostics, New Jersey for Australian patients; for IGF1 before the year 2000), Nichols Advantage Specialty System; Nichols Institute Diagnostics, San Juan Capistrano, CA; and after 2000, Immulite 2500 analyzer; Siemens Medical Solutions Diagnostics for American patients; Immulite 2000 analyser for Italian and Australian patients.

Imaging

Patients underwent head CT, pituitary MRI, and radio-labeled ⁹⁹Tc-methylene diphosphonate bone scintigraphy. BFD burden was quantified by bone scan score (BSS), a validated scoring system based on the scintigraphic analysis, ranging from 0 to 75 (18). BFD burden could be quantitatively and anatomically different from patient to patient, depending on mosaic distribution of fibrous dysplasia in MAS.

Head CT was used to determine optic nerve encasement, head circumference, sphenoid sinus opacification, facial asymmetry and malocclusion. In particular head circumference was determined radiographically from CT scans, using the perimeter tracing of oblique slices that correspond to the plane at which a clinical HC-tape measurement is secured, and macrocephaly was defined as greater than 2 SDS for age and gender (19). Pituitary MRI with gadolinium was used to detect the presence

of pituitary micro or macroadenoma and to follow their evolution. All MRI imaging were evaluated by two different radiologists of the same centre.

Audiology/otolaryngology

Baseline audiometric evaluations were conducted, and follow-up evaluations were annually performed at each visit. A four frequency (0.5/1/2/4 kHz) pure tone average greater than 20 dB hearing level was used as a marker for clinically significant hearing loss. Conductive hearing loss was present when the air conduction pure tone average was worse than the normal bone conduction pure tone average by greater than 10 dB.

Neuro-ophthalmology

Variables for optic neuropathy included: 1) best corrected visual acuity; 2) visual fields; 3) contrast vision; 4) colour vision; and 5) fundoscopic examination. Optic neuropathy was diagnosed in individuals with abnormal visual fields or an abnormality of at least two of the three other variables.

Pain

Chronic pain (present for at least 6 months) was assessed by asking “yes or no” regarding craniofacial district and other bone compartments, excluding acute pain related to fractures.

Intervention and efficacy

Management of patients was individualized, based on age, pubertal stage, other endocrinopathies, hormonal control, extension of BFD and comorbidities.

Treatment efficacy for GH hypersecretion was defined by an on-treatment IGF1 Z-score between -2 and $+2$ SDS. Subjects elected for pharmacotherapy were initiated on monthly octreotide, with dose escalation until the goal IGF1 Z-score was obtained or the maximum dose (30 mg/month) was reached. Subjects without appropriate IGF1 Z-score reduction on maximal dose octreotide were initiated on pegvisomant. Transphenoidal pituitary surgery and external beam irradiation were considered the final recourse in subjects with significant morbidity who failed to meet IGF1 efficacy criteria with maximal doses of both octreotide (30 mg/month) and pegvisomant (20 mg/day).

Thirty-seven patients with GH hypersecretion detected in all three cohorts (23 males and 14 females) were matched with 33 MAS controls (19 males and 14 females) without GH-IGF1 hyperactivity. Patients were matched for sex, age (range ± 7 yrs) and BSS (total BSS, range ± 5 scores and skull BSS, range ± 1 score).

Subjects with GH hypersecretion were divided in two subgroups based on time of treatment: patients treated before 16 yrs (Group A Early Intervention: 18 patients) and patients treated after 16 yrs or without therapy (Group B Late intervention: 19 patients).

Statistical Analysis

Data were gathered and analyzed using Excel (Microsoft Corporation, Redmond, U.S.A) and GraphPad Prism 6 (GraphPad software Inc., San Diego, CA). For continuous data *t test* comparisons were performed between two groups, whereas one-way *ANOVA analyses* assessed differences between multiple groups. Co-morbidities comparison between GH hypersecretion and MAS controls groups or between early and late intervention groups were performed by *Fisher's exact test*. A *Spearman correlation analysis* was done for GH-IGF1 and bone turn-over biochemical values with height SDS and head circumference SDS at diagnosis and at the end of follow-up. For all tests $p < 0.05$ was considered statistically significant.

Study approval

The study was approved by the Institutional Review Board of the National Institute of Dental and Craniofacial Research, NIH, Bethesda, USA; by Ethic Committee of Città della Salute, Torino, Italy; and by the Human Research Ethic Committee of the Royal Children's Hospital, Victoria, Australia. All subjects and/or their care-givers provided informed consent/assent.

Results

Study population of MAS patients

In these three cohorts, 37 patients with GH excess were identified (19% of the whole MAS population): 27/131 cases identified from the American cohort (20.6 %), 3/34 cases identified from the Italian cohort (8.8 %), 7/30 from the Australian cohort (23.3 %). Females constituted 37.8% of subjects with GH excess and 56% of the total cases.

GH excess was more frequent in males: 23/78 males 29.4% vs 14/17 females 11.9 % ($p = 0.002$); Mean age at diagnosis was 14.6 yrs (range 2.7-38 yrs.), there was no difference between males and females (14.44 ± 1.743 , $n=23$ and 15.00 ± 3.470 , $n=14$; $p = 0.873$). Eighteen patients were placed in Group A (Early intervention) while 19 patients in the Group B (Late Intervention). There was a significant difference in age at start of therapy between the 2 groups: 8.000 ± 0.6777 yrs., $n=18$ vs 20.92 ± 2.445 yrs, $n=19$ (R squared 0.4138; $p < 0.0001$).

The MAS control group included 33 MAS patients without GH excess (19 males and 14 females) matched for sex, age (mean age at evaluation 20.44 ± 1.852 yrs, $n=33$, vs 22.52 ± 1.759 yrs, $n=37$) ($p = 0.4184$) and total BSS (± 7 scores). Mean height SDS of patients with GH excess was $0.5866 \pm$

0.3993 SDS (range from -4.86 to 4.85 SDS), which was higher than in MAS controls (mean -1.412 ± 0.3236 SDS, range from -5.29 to 2.41 SDS; $p=0.0003$).

Hormonal and bone turn-over markers analysis at baseline

IGF1 SDS at diagnosis (mean 5.93 SDS) were significantly correlated to GH random levels (mean 11.49 ng/ml) (r Pearson 0.343; $p=0.03$), GH nadir after OGTT test (mean 18.6 ng/ml) (r Pearson 0.4226; $p=0.009$) and GH overnight nadir (mean 8.0 ng/ml) (r Pearson 0.5024; $p=0.008$).

At baseline evaluation, MAS patients in the control group showed mean random GH and IGF1 SDS levels in the normal range: 1.7 ng/ml and -0.9 SDS respectively. No further tests investigating the GH-IGF1 axis were performed in this group.

Hyperprolactinemia was found in 75.6% of subjects (28/37 patients) with GH excess, while 36.4% (12/33 patients) of MAS controls ($p=0.0035$). 28/40 were males (70%) while 13/40 were females (32.5%) ($p=0.0301$). Mean prolactin values are higher in the GH excess group (mean 62.34 ± 20.48 ng/ml $n=37$; vs 16.52 ± 2.624 ng/ml $n=33$ in MAS control group; $p=0.0397$).

Only 8 patients (21.62%) displayed also clinical manifestations: 3 patients showed a hypogonadotropic hypogonadism, 3 others a hypogonadotropic hypogonadism and secondary hypothyroidism, 1 subject had a secondary hypothyroidism, whereas the last one a delayed puberty. Bone turn-over markers (alkaline phosphatase and osteocalcin) at baseline were higher in GH excess group than in the control group: mean ALP 865.7 ± 128.1 UI/l, ($n=36$) vs 440.2 ± 67.99 UI/l, ($n=33$) ($p=0.0057$); mean osteocalcin 157.8 ± 22.27 ng/ml, ($n=25$) vs 126.1 ± 15.40 ng/ml, ($n=31$), $p=0.2339$).

Imaging assessment at baseline

All GH excess MAS patients had craniofacial, and appendicular skeleton FD.

Mean skull BSS was 3.22 in group A (Early treatment), 3.47 in group B (Late treatment) and 2.93 in the MAS control group, where score 0 means absence of fibrous dysplasia and score 4 means 100% of involvement of cranio-facial region as previously described (ANOVA Comparison $p=0.09$) (17). Mean total BSS was 35.86 in group A, 40.48 in group B and 36.97 for the MAS control group, where 0 score means absence of FD and 75 score means 100% skeletal involvement. (ANOVA Comparison $p=0.798$).

Mean head circumference SDS, was significantly higher in GH excess group compared with MAS controls group: 4.025 SDS (ranging from -3.41 to 22.56 SDS) vs 0.683 SDS (ranging from -2.16 to 6.20 SDS) ($p<0.0001$); consequently macrocephalic patients (head circumference $> +2$ SDS) were more numerous in GH hypersecretion group: 29/37 patients (78.37%) vs 6/33 patients (18.18%) ($p<0.0001$).

The prevalence of sphenoid sinus obliteration and optic nerve encasement did not significantly differ in the GH excess group compared with the MAS control group: 32/37 (86.48%) vs 27/32 (84.37%) ($p=1.00$); 33/37 (89.18%) vs 28/33 (84.84%) ($p=0.7257$).

Pituitary MRI with gadolinium was performed in all patients with GH excess: 15/37 subjects (40.54%) showed one or more adenohypophysis microadenomas, 6/37 (16.22%) one or more macroadenomas (main diameter >1 cm), 2/37 (5.41%) showed abnormal enhancement of the pituitary i.e. indirect sign of mammosomatotropic pituitary hyperplasia, in 12/37 patients (37.84%) adenohypophysis was normal.

Evaluation for Comorbidities

The mean age at evaluation was not significantly different for the four compared groups: in the Late treatment group was 27.31 ± 2.875 yrs, ($n=18$) while in Early treatment group 24.33 ± 2.719 yrs, ($n=19$) ($p=0.4566$); in the GH excess group was 22.52 ± 1.759 yrs, ($n=37$) while in the MAS control group 20.44 ± 1.852 yrs, ($n=33$) ($p=0.4184$).

The risk of optic neuropathy, hearing deficit and facial asymmetry were higher in GH excess group compared to MAS controls: 11/37 patients (29.72%) vs 3/33 patients (9.09%) ($p=0.039$) (Odds ratio 4.231); 18/37 patients (48.64%) vs 8/33 patients (24.24%) ($p=0.0481$) (Odds ratio 2.961); 35/37 patients (94.59%) vs 24/33 patients (72.72%) ($p=0.0192$).

By contrast no difference was found for malocclusion and chronic cranio-facial and long bone pain: 29/37 subjects (78.37%) vs 23/33 subjects (72.72%) ($p=0.7807$); 15/37 subjects (40.54%) vs 14/33 subjects (42.42%) ($p=1.000$); 27/37 subjects (72.97%) vs 29/33 subjects (87.87%) ($p=0.1443$) respectively.

At the end, the association between tumors and GH-IGF axis hyperactivity was evaluated although not systematically screened in all patients; in particular we have to consider that not all patients were screened for gastro-intestinal pathology, like in the Australian cohort (20). During follow-up in GH hypersecretion group a testicular Leydig cells tumor, two cranio-facial osteo-sarcomas, a breast carcinoma, five gastro-intestinal polyps, one gallbladder polyp were reported; while only one gastro-intestinal polyp was identified in the MAS control group: 9/37 patients vs 1/33 controls, Odds ratio 15.24; ($p=0.0173$); no malignant tumors were notified in MAS control group.

Impact of therapy on comorbidities

Twenty-nine patients with GH excess started pharmacotherapy with long acting somatostatin analogues (ocreoite 10-30 mg/month). Monotherapy was effective to reduce IGF1 SDS into normal

range in 16/29 patients (55.17%). In 7/13 patients, without IGF1 control on octreotide, GH receptor antagonist was added (pegvisomant 10-20 mg/day). This medical treatment was effective in 5/7 patients and decreased IGF1 SDS without normalization in the other 2 cases (from 3.7 SDS to 2.3 SDS and contemporary with pituitary radiotherapy, from 4 SDS to 2.5 SDS, respectively).

Two patients previously described in a NIH case series, were candidates for transphenoidal hypophysectomy after failing pharmacotherapy (mean age of medical treatment 3.6 years) (14). One patient had a IGF1 SDS reduction, but unfortunately he died for a post-operative intraventricular hemorrhage, also related to bleeding of bone fibrous dysplasia; after surgery, one patient developed hypopituitarism, without IGF1 SDS normalization (IGF1 2.5 SDS). One patient after failing octreotide was treated for 2.5 years with pegvisomant monotherapy, but due to low compliance was a candidate for pituitary radiotherapy; after six years no IGF1 SDS target was reached.

Overall, pharmacotherapy (octreotide 10-30 mg/month or with pegvisomant 10-20 mg/day) was effective in IGF1 normalization ($-2\text{SDS} < \text{IGF1} < +2\text{SDS}$) in 21/29 patients (72.4%) with good compliance with the regimen. Post-treatment IGF1 SDS were significantly reduced: mean pre-therapy 4.260 ± 0.9246 SDS (n=29) vs mean post-therapy 0.7264 ± 0.3370 SDS (n=29) ($p=0.0009$). We analyzed impact of early medical therapy for GH hypersecretion in the paediatric age group (under 16 years of age) respect to late treatment group. Odds ratio of optic neuropathy for late treatment was 4.5: 9/19 patients (47.36%) in the late intervention group compared with 3/18 patients (16.66%) in early intervention group ($p=0.0491$). In the late treatment group there was a trend toward increased risk for hearing deficit (Odds ratio 1.746; $p=0.5148$), facial asymmetry (Odds ratio 7.00, $p=0.2342$), dental malocclusion (Odds ratio 2.857, $p=0.4048$) and tumour development (Odds ratio 3.692, $p=0.2320$), however this did not reach statistical significance.

Medical therapy appeared to be effective at preventing growth of pituitary adenomas growth: macroadenomas were identified in 6/19 subjects in the late therapy group compared with 1/18 subjects in early therapy group (Odds ratio 7.846; $p=0.050$).

Discussion

The prevalence of GH hypersecretion in our cohorts was 19 %, more frequent in males compared to females, unlike isolated acromegaly (21), with a wide range of diagnosis age from infancy to first adult age.

Unlike isolated acromegaly, increased height is not a reliable predictive sign and the final height is generally normal, because it is the result of multiple endocrinopathies, in particular precocious puberty and hyperthyroidism, and it depends on the involvement of long bones and vertebral column by fibrous dysplasia. In our cohorts, patients with GH excess were significantly taller compared to MAS controls, although the mean height was under 2 SDS. FD involving the skull base was present in all patients with GH-IGF axis hyperactivity, so it is an important predictive sign of GH excess, nevertheless it is very common in MAS.

For GH hypersecretion diagnosis, random GH and basal IGF1 investigations are mandatory and are used for routine screening; however, when the basal tests are not conclusive and the clinical suspicion is high, overall in patients with progressive craniofacial asymmetry, GH suppression test and frequent overnight GH sampling can be utilized as confirmatory tests. In all patients with GH excess we found two pathologic basal tests (IGF1 SDS and random GH) at least, or one basal test (IGF1 SDS or random GH) and one stimulating test (GH suppression OGTT, and frequent overnight GH); since IGF1 SDS were significantly related to random GH, nadir GH post OGTT and overnight nadir GH, it represents a valuable but not sufficient screening test. Thus, frequent sampling has been to be established as accurate tool to detect abnormal GH production in acromegalic adults. In children it is a common and validated method to study GH neurosecretory dysfunction related to short stature (22,23). Pituitary MRI is not useful for the diagnosis because the absence of adenomas does not exclude diffuse somatotroph hyperplasia: in half of cases imaging was normal or diffuse enhancement on T1 weighted was identified.

This study confirms the starting hypothesis: GH-IGF1 hyperactivity impacts MAS BFD, in particular in the craniofacial region, with craniofacial expansion and deformity (16). These effects are reflected systemically by increased serum bone turn-over markers. To evaluate craniofacial expansion we compared head circumference SDS, and found this was significantly higher in GH excess patients. Functionally this results in a higher risk not only of optic neuropathy, as previously reported but also of hearing deficit: we can speculate that it may be caused by nerve traction from craniofacial expansion deformity and/or nerve canal compression. For hearing deficit it there may be an alteration in middle ear and Eustachian tube dynamics by FD (24,25). Finally adenoid and tonsillar hypertrophy, reported in iatrogenic acromegaly, may also contribute (26).

The pathogenesis of BFD expansion is related to stromal cell proliferation and osteoclast invasion of normal areas of bone. In acromegalic patients without MAS, GH excess leads to linear growth of

bones, including craniofacial bones, through IGF1 effects on bone forming mesenchymal cells (27,28). Expansion of BFD in MAS has got an exponential growth because is the result of a combination of Gs-alpha hyperactivation and IGF1 overproduction (16).

The prevalence of sphenoid sinus obliteration, optic nerve encasement and malocclusion did not reach significative difference in the GH excess group compared with the MAS control group, although a negative trend was present for patients with GH hypersecretion.

In addition GH hypersecretion could be an important risk factor for MAS-associated tumors. This is probably the multifactorial result of Gs-alpha mutation, GH-IGF1 hyperactivity, other endocrinopathies, radiotherapy, and further gene mutations. Precocious puberty, due to hyperestrogenism, has been reported on 71% of our patients with neoplasia. *In vitro* and in murine models GH3 somatotroph cells or FRTL-5 thyroid cells, trasfection with Gs-alpha mutant induces constitutive activation of the cAMP pathway and activates mitogenic signals, leading to hyperplasia, and respectively pituitary adenomas and thyroid toxic adenomas (29,30). In thyroid carcinoma molecular analysis revealed that foci of malignancy and adjacent areas of normal thyroid harbored the same activating mutations of Arg201 in GNAS gene: these finding suggesting that additional mutations (RET/PTC e k-RAS) or epigenetic events for neoplastic “multistep-process” are necessary (31,32). In MAS sarcomatous degeneration of dysplastic bone may occur and a role for radiotherapy has also been suggested (33).

Pain is probably related to other mechanism like bone-turnover status, pathological fractures, bisphosphonates therapy and hypophosphatemia and/or subjective perception.

The high prevalence (75%) of hyperprolactinemia in our case series indicate that these two endocrinopathies are significantly associated, also given the male prevalence and the embryological origin (mammosomatotroph pituitary hyperplasia) (34,35). The phenotypic expression of MAS hyperprolactinemia is apparently lower compared to isolated hyperprolactinemia: in our cohorts only 25% of these patients developed hypogonadotropic hypogonadism or central hypothyroidism, maybe because GSalpha related hormonal hypersecretion is responsible for continuing apparently normal gonadal function.

Octreotide alone was effective in IGF1 normalization in half of the patients, while combined therapy with octreotide and pegvisomant was effective in two third of patients. Medical therapy significantly decreases risk of optic neuropathy and growth of pituitary adenomas, when it was performed during paediatric age, demonstrating that somatostatin analogs with or without GH receptor antagonist represent an effective first line treatment for MAS GH excess (16,36). Pituitary surgery is technically difficult in patients with MAS, due to thickness of the cranial dysplasia of the

skull base, particularly for sphenoid sinus obliteration with a high risk of hemorrhage given the high vascularity of BFD. Total hypophysectomy was performed in two cases with diffuse somatolactotroph hyperplasia of pituitary gland, with subsequent panhypopituitarism: one died due to post-operative hemorrhage, a second one had persistent elevated IGF1 levels. These aspects, confirmed surgery as second line treatment that should be reserved for MAS patients with intractable disease not responsive to pharmacotherapy (14,37). Radiotherapy was performed in only one case without IGF1 SDS control, after 6 years follow-up. However, given the risk of sarcomatous transformation and hypopituitarism, it should be reserved to extremely severe GH excess resistant to pharmacotherapy and in patients not candidates for surgery, as third line treatment (38).

This study further points out that GH-IGF1 hyperactivity increases risk of morbidities in MAS. The medical therapy in such condition is effective in normalizing IGF1 in most patients, and the early treatment during paediatric age seems to decrease optic neuropathy and GH adenomas growth.

Abbreviations

BFD: bone fibrous dysplasia

MAS: McCune-Albright Syndrome

Gsalpha: α -subunit of the Gs stimulatory protein

FGF23: fibroblast growth factor 23

GH: growth hormone

IGF1: insulin like growth factor 1

SDS: standard deviation score

OGTT: oral glucose tolerance test

ALP: alkaline phosphatase

MRI: magnetic resonance imaging

CT: computed tomography

BSS: body scan score

NSAIDS: non steroidal anti-inflammatory drugs

NIH: National Institute of Health

RANK: receptor activator of Nuclear Factor KB

RANKL: receptor activator of Nuclear Factor KB ligand

OPG: osteoprotegerin

Figures legend

Fig.1 Linear correlation IGF1 SDS - GH random (A) - GH nadir OGTT (B) - GH night nadir (C)

Fig.2 Alkaline phosphatase levels in GH excess group vs normal GH group

Fig.3 Head circumference SDS in GH excess group vs normal GH group

Fig.4 IGF1 SDS pre-treatment vs post treatment

Table 1 Flow-chart of GH excess therapy

Table 2 Diagnostic Flow-chart of GH excess

Table 3 Principal baseline data and comorbidities of GH patients for the three different cohorts pre-therapy

References

1. Collins MT, Riminucci M, Bianco P. Fibrous dysplasia. *Primer on the metabolic bone diseases and disorders of mineral metabolism*. 2013; 1:786-793.
2. Lichtenstein L, Jaffe, H. Fibrous dysplasia of bone: a condition affecting one, several or many bones, the graver cases of which may present abnormal pigmentation of skin, premature sexual development, hyperthyroidism or still other extraskelatal abnormalities. *Arch Pathol* 1942; 33:777-816.
3. Dumitrescu CE, Collins MT. McCune-Albright syndrome. *Orphanet journal of rare diseases*. 2008 19:3-12.
4. Albright F, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas, of pigmentation, and endocrine dysfunction, with precocious puberty in females: report of 5 cases. *The New England journal of medicine*. 1937; 216:727-746.
5. Weinstein LS, Shenker A, Gejman PV, Merino MJ, Friedman E, Spiegel AM. Activating mutations of the stimulatory G protein in the McCune-Albright syndrome. *The New England journal of medicine*. 1991; 325:1688-1695.
6. Schwindinger WF, Francomano CA, Levine MA. Identification of a mutation in the gene encoding the alpha subunit of the stimulatory G protein of adenylyl cyclase in McCune-Albright syndrome.

- Proceedings of the National Academy of Sciences of the United States of America*. 1992; 89:5152-5156.
7. Happel R. The McCune-Albright syndrome: a lethal gene surviving by mosaicism. *Clinical genetics*. 1986; 29: 321-324.
 8. Arrigo T, Pirazzoli P, De Sanctis L, Leone O, Wasniewska M, Messina MF, De Luca F. McCune-Albright syndrome in a boy may present with a monolateral macroorchidism as an early and isolated clinical manifestation. *Hormone Research*. 2006; 65: 114-119
 9. Robey PG, Kuznetsov S, Riminucci M, Bianco P. The role of stem cells in fibrous dysplasia of bone and the McCune-Albright syndrome. *Pediatr Endocrinol Rev* 2007; 4:386-394.
 10. Riminucci M, Fisher LW, Shenker A, Spiegel AM, Bianco P, Gehron Robey P. Fibrous dysplasia of bone in the McCune-Albright syndrome: abnormalities in bone formation. *The American journal of pathol*. 1997; 151:1587-1600.
 11. Bianco P, Kuznetsov SA, Riminucci M, Fisher LW, Spiegel AM, Robey PG. Reproduction of human fibrous dysplasia of bone in immunocompromised mice by transplanted mosaics of normal and Gsalpha-mutated skeletal progenitor cells. *The Journal of clinical investigation*. 1998; 101:1737-1744.
 12. Boyce AM, Collins MT. Fibrous Dysplasia/McCune-Albright Syndrome. *GeneReviews: University of Washington, Seattle* 2015; 1993-2016.
 13. Tessaris D, Corrias A, Matarazzo P, De Sanctis L, Wasniewska M, Messina MF, Vigone MC, Lala R. Thyroid abnormalities in children and adolescents with McCune-Albright syndrome. *Horm Res Paediatr*. 2012; 78:151-157.
 14. Salenave S, Boyce AM, Collins MT, Chanson P. Acromegaly and McCune-Albright syndrome. *J Clin Endocrinol Metab*. 2014; 99:1955-1969.
 15. Cutler CM, Lee JS, Butman JA, FitzGibbon EJ, Kelly MH, Brillante BA, Feuillan P, Robey PG, DuFresne CR, Collins MT. Long-term outcome of optic nerve encasement and optic nerve decompression in patients with fibrous dysplasia: risk factors for blindness and safety of observation. *Neurosurgery*. 2006; 59:1011-1017.
 16. Boyce AM, Glover M, Kelly MH, Brillante BA, Butman JA, Fitzgibbon EJ, Brewer CC, Zalewski CK, Cutler Peck CM, Kim HJ, Collins MT. Optic neuropathy in McCune-Albright syndrome: effects of early diagnosis and treatment of growth hormone excess. *J Clin Endocrinol Metab*. 2013; 98: 126-134.
 17. Yao Y, Liu Y, Wang L, Deng K, Yang H, Lu L, Feng F, Xing B, You H, Jin Z, Wang R, Pan H, Chen S, Zhu H. Clinical characteristics and management of growth hormone excess in patients with McCune-Albright syndrome. *Eur J Endocrinol*. 2017; 176:295-303.
 18. Collins MT, Kushner H, Reynolds JC, Chebli C, Kelly MH, Gupta A, Brillante B, Leet AI, Riminucci M, Robey PG, Bianco P, Wientroub S, Chen CC. An instrument to measure skeletal

- burden and predict functional outcome in fibrous dysplasia of bone. *J Bone Miner Res.* 2005; 20: 219-226.
19. Vorperian HK, Durtschi RB, Wang S, Chung MK, Ziegert AJ, Gentry LR. Estimating head circumference from pediatric imaging studies an improved method. *Acad Radiol* 2007; 14:1102-1107.
 20. Wong SC, Zacharin M. Long-term health outcomes of adults with McCune-Albright syndrome. *Clinical Endocrinol.* 2017; 12. doi: 10.1111/cen.13419
 21. Andersen M. Management of endocrine disease GH excess: diagnosis and medical therapy. *Eur J Endocrinol.* 2013; 170:31-41.
 22. Bajuk Studen K, Barkan A. Assessment of the magnitude of growth hormone hypersecretion in active acromegaly: reliability of different sampling models. *J Clin Endocrinol Metab.* 2008; 93:491-496.
 23. August GP, Hung W, Sonis W, Mendelson W, Bercu BB. Growth hormone neurosecretory dysfunction. A treatable cause of short stature. *JAMA.* 1984; 251:2223-2230.
 24. Lee JS, FitzGibbon E, Butman JA, Dufresne CR, Kushner H, Wientroub S, Robey PG, Collins MT. Normal vision despite narrowing of the optic canal in fibrous dysplasia. *N Engl J Med.* 2002; 347: 1670-1676.
 25. Cutler CM, Lee JS, Butman JA, Fitz Gibbon EJ, Kelly MH, Brillante BA, Feuillan P, Robey PG, Dufresne CR, Collins MT. Long-term outcome of optic nerve encasement and optic nerve decompression in patients with fibrous dysplasia: risk factors for blindness and safety of observation. *Neurosurgery.* 2006; 59:1011-1017.
 26. Gerard JM, Garibaldi L, Myers SE, Aceto T Jr, Kotagal S, Gibbons VP, Stith J, Weber C. Sleep apnea in patients receiving growth hormone. *Clin Pediatr.* 1997; 36:321-326.
 27. Ebner FH, Kürschner V, Dietz K, Bültmann E, Nägele T, Honegger J. Craniometric changes in patients with acromegaly from a surgical perspective. *Neurosurg Focus.* 2010; 29:E3.
 28. Kojima I, Iikubo M, Kobayashi A, Ikeda H, Sakamoto M, Sasano T. High serum levels of IGF-I contribute to promotion of endochondral ossification in mandibular condyle and cause its specific elongation in acromegaly-like rats. *Horm Metab Res.* 2008; 40:533-538.
 29. Ham J, Ivan M, Wynford-Thomas D, Scanlon MF. GH3 cells expressing constitutively active Gs alpha (Q227L) show enhanced hormone secretion and proliferation. *Mol Cell Endocrinol* 1997; 127:41-47.
 30. Muca C, Vallar L. Expression of mutationally activated G alpha s stimulates growth and differentiation of thyroid FRTL5 cells. *Oncogene* 1994; 9:3647-3653.
 31. Collins MT, Sarlis NJ, Merino MJ, Monroe J, Crawford SE, Krakoff JA, Guthrie LC, Bonat S, Robey PG, Shenker A. Thyroid carcinoma in the McCune-Albright syndrome: contributory role of activating Gs alpha mutations. *J Clin Endocrinol Metab.* 2003; 88:4413-4417.

32. Wood LD, Noë M, Hackeng W, Brosens LA, Bhaijee F, Debeljak M, Yu J, Suenaga M, Singhi AD, Zaheer A, Boyce A, Robinson C, Eshleman JR, Goggins MG, Hruban RH, Collins MT, Lennon AM, Montgomery EA: Patients with McCune-Albright syndrome have a broad spectrum of abnormalities in the gastrointestinal tract and pancreas. *Virchows Arch.* 2017; 470:391-400.
33. Hansen MR, Moffat JC. Osteosarcoma of the Skull Base after Radiation Therapy in a Patient with McCune-Albright Syndrome: Case Report. *Skull Base* 2003; 13:79-83.
34. Christoforidis A, Maniadaki I, Stanhope R. McCune-Albright syndrome: growth hormone and prolactin hypersecretion. *J Pediatr Endocrinol Metab* 2006; 19:623-625.
35. Kovacs K, Horvath E, Thorner MO, Rogol AD: Mammosomatotroph hyperplasia associated with acromegaly and hyperprolactinemia in a patient with the McCune-Albright syndrome. A histologic, immunocytologic and ultrastructural study of the surgically-removed adenohypophysis. *Arch A Pathol Anat Histopathol* 1984; 403:77-86.
36. Akintoye SO, Kelly MH, Brillante B, Cherman N, Turner S, Butman JA, Robey PG, Collins MT: Pegvisomant for the treatment of gsp-mediated growth hormone excess in patients with McCune-Albright syndrome. *J Clin Endocrinol Metab* 2006; 91:2960-2966.
37. Madsen H, Borges MT, Kerr JM, Lillehei KO, Kleinschmidt-Demasters BK. McCune-Albright syndrome: surgical and therapeutic challenges in GH-secreting pituitary adenomas. *J Neurooncol* 2011; 104:215-224.
38. Ruggieri P, Sim FH, Bond JR, Unni KK. Malignancies in fibrous dysplasia. *Cancer* 1994; 73:1411-1424.

Table 1 Flow-chart of GH excess therapy

Table 2 Diagnostic Flow-chart of GH excess

Table 3 Principal baseline data and comorbidities of GH patients for the three different cohorts pre-therapy

Baseline factors	Italian cohort	American cohort	Australian cohort
Sex	3 males	14 males, 13 females	6 males, 1 female
Mean age at MAS diagnosis	1.26 years (range 0.5 - 2)	4.89 years (range 0.8 - 14)	8.7 years (range 0.4 - 30)
Mean age at iperGH diagnosis	18.2 years (range 10.3 - 25)	12.7 years (range 2.7 - 35.8)	20.4 years (7.2 - 36)
Mean height males cm/SDS	159.76 cm; 0.68 SDS (range 144.6 - 171.2 cm; -1.85 - 2.94 SDS)	147.35 cm; 0.58 SDS (range 83 - 199.4 cm; -3.9 - 3.72 SDS)	153.31 cm; - 0.75 SDS (range 137 - 177 cm; -3.08 - 2.39 SDS)
Mean height females cm/SDS	-	139.23 cm; 1.25 SDS (range 99 - 169 cm; -2.34 - 4.45 SDS)	158 cm; -0.8 SDS
GH random ng/ml	7.54 (2.74 - 10.30)	15.65 (2.8 - 57)	6.98 (2.1 - 16)
GH OGTT suppression test	3.47 (2.04 - 5.79)	9.8 (1 - 60.2)	21.12 (6.15 - 41.9)
Frequent GH overnight nadir	3.06	5.42 (0.4 - 32.2)	-
IGF1 SDS	6.65 (4.9 - 8.7)	4.47 (-1.2 - 19.37)	3.19 (-1.8 - 13.25)
Prolactin ng/ml	31.8 (7.3 - 73.3)	77.1 (13 - 740)	18.2 (4.4 - 38)
Head circumference SDS	3.98 (2.21 - 6.01)	3.85 (-3.41 - 22.56)	4.6 (0.95 - 10.72)
Alkaline phosphatase U/l	2637 (1647 - 3316)	750.38 (258 - 2950)	535 (176 - 1318)
Osteocalcin ng/ml	-	172.4 (43.6 - 390)	81 (36 - 193.8)
Skull scan score	3.66 (3 - 4)	3.18 (1 - 4)	3.85 (3 - 4)
Total bone scan score	21.83 (15.75 - 32)	37.43 (3.76 - 75.02)	50.89 (9.38 - 75.015)
Pituitary adenomas at magnetic resonance imaging (MRI)	1/3 (33.33%)	19/27 (70.37%)	1/7 (14.28%)

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