DR SZE CHOONG WONG (Orcid ID : 0000-0003-2845-6555)

Article type : 1 Original Article - UK, Europe

Long Term Health Outcomes Of Adults With McCune Albright Syndrome

Short running title: Adults with McCune Albright Syndrome

SC Wong ¹, M Zacharin ^{2,3}

¹ Developmental Endocrinology Research Group, Royal Hospital for Children,
Glasgow, United Kingdom

² Department of Endocrinology, The Royal Children's Hospital, Melbourne, Australia

³ Centre for Hormone Research. Murdoch Children's Research Institute, Melbourne,
Australia

Address for correspondence:

Prof M Zacharin,
Dept of Endocrinology, Murdoch Children's Research Institute,
The Royal Children's Hospital,
Flemington Road, Parkville,
Victoria, 3052, Australia
Tel: +61 3 93455951
Email: margaret.zacharin@rch.org.au

Acknowledgements: We would like to acknowledge the help of Lindy Tukavkin for assistance with data collection.

Key words: Bisphosphonate, café au lait, cancer, fertility, fibrous dysplasia, gastrointestinal polyps, growth hormone excess, platelet dysfunction, thyrotoxicosis,

This is the author manuscript accepted for publication and has undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process, which may lead to differences between this version and the Version of Record. Please cite this article as [doi: 10.1111/cen.13419](https://doi.org/10.1111/cen.13419)

This article is protected by copyright. All rights reserved

SUMMARY

Context: McCune Albright Syndrome (MAS) is associated with numerous health problems. Comprehensive long term health problems of adults with MAS are less well defined in the literature.

Objective: Our objective is to report comprehensive health outcomes of adults with MAS (> 18 years).

Design: Retrospective case note review of 16 adults with MAS managed by one clinician. Results expressed as median (range)

Results: The study included 16 adults (7 males) with MAS. Median current age is 29 years (20, 46). Twelve out of 16 had craniofacial fibrous dysplasia with 5/12 (42%) with progressive facial asymmetry. Growth hormone excess was observed in 6/16 (38%) and T3-toxicosis in 5/16 (31.3%). Six of the 7 men (86%) had abnormalities on testicular ultrasound with one man exhibiting marked atrophy of germ and Sertoli cells with reduction in spermatogenesis. Six of the 16 (38%) had cardio-respiratory complications including high output cardiac failure (n,3) hypertension (n,2) and one man with congestive cardiac failure and restrictive lung disease. Six of 8 (66%) who had screening endoscopy for upper gastrointestinal polyps show increasing numbers of polyps, with benign histology to date. One woman with a previous history of early puberty presented with early aggressive breast carcinoma, which was positive for GNAS. Two patients had GNAS positive muscle myomas. Platelet dysfunction with bleeding tendency responsive to platelet transfusion during surgery was seen in four.

Conclusion: A range of complex health problems is encountered in adults with MAS. These have important implications for transition of patients with MAS and adult care. Long term cancer risk is currently unknown but requires careful follow-up.

INTRODUCTION

McCune Albright Syndrome (MAS), is due to a somatic mutation in the G protein Guanine Nucleotide Binding α subunit (GNAS) gene, associated with cafe au lait marks, polyostotic fibrous dysplasia (FD), gonadotropin independent precocious puberty and other endocrine gland hyper function. Whilst management in childhood generally focuses on treatment of fibrous dysplasia and early puberty^{1,2}, adult focus shifts to challenging problems of endocrine hyper function especially acromegaly and

1 thyrotoxicosis.^{3,4} Even though appendicular fibrous dysplasia usually stabilizes by
2 late adolescence, adults with MAS often suffer significant pain and poor mobility due
3 to existing lesions, together with worsening skull deformity, aggravated by
4 acromegaly. In addition, endocrine hyperfunction and other health problems may also
5 complicate overall skeletal management..

6 Emerging evidence suggests that gonadal abnormalities in men and women
7 may affect fertility⁵⁻⁷. Thyroid cancer⁸, breast carcinoma⁹ and malignant sarcoma¹⁰
8 have been reported in MAS. There may also be a risk of gonadal⁵ and
9 gastrointestinal tumors^{11,12}, with various types of gastrointestinal polyps reported in
10 MAS.^{11,12} It is therefore imperative that clinicians providing adult care to these
11 patients are aware of the spectrum of these problems. There are few reports of
12 comprehensive long term outcomes and evolving health problems of adults with
13 MAS.

22 **SUBJECTS AND METHODS**

23 A retrospective case note review was conducted for adults with MAS (aged $\geq$
24 18 years) to report long term comprehensive health outcome in adulthood, regarding
25 fibrous dysplasia, thyroid abnormalities, growth hormone (GH) excess, testicular
26 abnormalities and other lesions known to be associated with the underlying condition.
27 Case records of the private practice of one of the authors (MZ) were used to obtain
28 this information. The majority were also previously managed by the same clinician
29 during paediatric care. All investigations included were conducted as part of clinical
30 monitoring of the patients. As we utilized data collected in routine clinical practice,
31 ethical approval was not required. This report of clinical experience of long term adult
32 outcome of MAS is unique in that these patients were managed by one single
33 endocrinologist but not a unit with specialist research interest in MAS.

RESULTS

General characteristics

Sixteen adults (7 males) with MAS, median age 31.5 years (22,49) and median time since diagnosis of 25 years (5,34) were included in this study [Table 1]. Fracture or skeletal symptoms were the commonest initial presenting complaint in our cohort. Café au lait spots were present in 15 individuals (94%). Five of the 16 (31%) were diagnosed after age 16 years of age. Three of the 5 were women who had previous history of early puberty/menarche (breast development aged 6-7 years and menarche from age 9 years); including 2 with typical café au lait spots (Patients 13 and 16). However, a diagnosis of MAS was not considered in childhood. Genetic confirmation was available in nine of the 16 (56%), with GNAS mutation found in peripheral blood in all of these. Twelve individuals had adult height measurements and six of the 12 (50%) had height SDS < -2.0 (Patients 1, 2, 4, 5, 7 and 13). Patient 2 and 5 had adult height SDS of -4.0 and -5.0, respectively, due to scoliosis and severe FD.

Fibrous dysplasia and bone

Eleven of 16 (69%), had polyostotic FD. Three (19%) with FD involvement in the spine had panostotic FD [Table 2]. Twelve of 16 (75%) had craniofacial FD, 5/12 (42%) with significant facial asymmetry which continued to progress in adulthood (Patients 1, 2, 4, 5, 7), with severe disfigurement requiring reconstructive/remodeling surgery to the maxilla and mandibular areas in patients 1, 2 and 4. Of these, patients 2, 5, 7 have concomitant acromegaly but patients 1 and 5 have equally severe progression of facial changes. Patient 5 has severe deformity with difficulty in opening his mouth but is too unwell to contemplate surgery. Anaesthetic risk was

1 extremely high in all , due to limited access incurred by facio- mandibular FD. Platelet
2 cover prevented catastrophic blood loss in patient 1. Spontaneous migration of long
3 term intramedullary rods in the humeri of patients 2 and 5, through the distal end and
4 through skin, have required replacement and only recently observed.

5 Regular bisphosphonate was not used in this cohort in adulthood but
6 intermittent, short term treatment with intravenous (IV) pamidronate (1 mg/kg/dose)
7 or zoledronate (0.04 mg/kg/dose) was utilized successfully to treat chronic
8 generalized bony pain (Patients 4, 5, 13 and 15), quadrant visual field defect with
9 stable resolution of visual fields over >10 years (Patient 7: treated between age 18-
10 20 and again at age 32) and severe T4-5 nerve root compression neuropathy
11 (Patient 13: treated with 3 doses of zoledronate aged 35 years). Use of IV
12 bisphosphonate provided virtually complete resolution of pain in individuals 4, 5 and
13 13 for 3-5 years or more. Patient 15 continued to have intermittent root pain related
14 to extensive FD at T12. All of the 3 with pan-ostotic FD and 3/11 (27%) with
15 polyostotic FD had restricted mobility requiring intermittent use of wheelchair and/or
16 crutches. Mechanical back pain related to extreme scoliosis required additional
17 analgesia in patient 4. Some restriction of daily living was present in several severely
18 affected individuals, with use of crutches , wheelchair and/or family assistance in five.
19 (detailed in table 2).

20 Three of the 16 (19%) had significant phosphate wasting requiring phosphate
21 supplementation, based on plasma phosphate measurements. Fractures through FD
22 lesions in long bones were recorded in 4 individuals as adults, all after significant
23 trauma (Patient 2: neck and arm from motor vehicle accident, Patient 4: forearm,
24 Patient 7: femur and Patient 15: arm).

26 *Growth hormone excess*

27 Six of the 16 (38%) have biochemical evidence of growth hormone (GH)
28 excess, the majority diagnosed as adults although the youngest individual was
29 diagnosed at age 8 years (Patient 2) [Table 3]. Prolactin levels were either marginally
30 raised or normal. Pituitary tumour was the presenting feature of one patient which
31 was GH secreting and stained for somatotrophs (Patient 13). No tissue was sent for
32 genetic analysis as endocrine involvement only occurred later as it was not
33 recognized that she has MAS. Pituitary magnetic resonance imaging (MRI) revealed
34 diffuse pituitary enlargement in two patients with severe craniofacial FD. Pituitary
35 fossa could not be adequately visualized in two patients due to severe FD (Patient 2
36 and 5) and micro adenoma was reported in one (Patient 3).

Two with biochemical evidence of GH excess but currently "normal" insulin like growth factor-1 (IGF-1 levels) of less than + 2.0 standard deviation (SD), and no clinical signs or symptoms have not yet been commenced on treatment (Patient 1 and 5). IGF-1 levels of patient 5 may be relatively low due to severe cardio-respiratory ill health. Treatment for the others was with long acting octreotide and cabergoline. One patient was changed to pasireotide due to poor biochemical control of GH excess, on cabergoline and sandostatin LAR, but rapidly developed poorly controlled diabetes mellitus with massive insulin requirements >3units/kg/day plus maximal metformin (Patient 2). Control of GH excess did not improve so treatment reverted back to cabergoline and octreotide, with significant reduction in insulin requirement but still persistent diabetes mellitus. IGF-1 levels normalized in one (Patient 3), remained in the high normal range (+1.0 to +2.0 SD) in one (Patient 5) and remained significantly elevated in two (Patient 2 and 13). Patient 2 has recently commenced Pegvisomant.

Thyroid

Five of the 16 (31.3%) developed T3 toxicosis, 3 presenting in late adolescence and two in adulthood [Table 3]. All were negative for TSH receptor antibody. All were initially managed with anti-thyroid drugs, followed by definitive ablative radioiodine (I131). All had subsequent thyroxine replacement and no recurrence of T3 toxicosis has occurred to date. All five with T3 toxicosis had evidence of abnormal thyroid morphology on imaging, 2/4 with hot nodule on uptake scan (Patients 2 and 5). Seven euthyroid individuals had thyroid ultrasound and 5/7 (71%) had evidence of abnormal thyroid morphology on imaging. In total 11/16 had thyroid ultrasound and 9/11 (82%) had evidence of abnormalities. Two required surgery for large multinodular goitre (patient 13) and thyroid nodule (patient 16) with histopathology showing benign follicular adenoma. For those who had I131, complete ablation of the thyroid were performed, to minimize risk of later malignancy¹³.

Gonads

Ten of the 16 (62.5%) had evidence of early puberty [Table 2]. Seven of the 9 (78%) women had a previous history of early puberty with onset of breast development reported between 4-8 years. Only one was previously treated with tamoxifen by another clinician (Patient 11). Two of the women have had spontaneous pregnancies to date (Patients 13 and 14).

Three of the 7 (43%) men had evidence of early puberty (Patient 1, 2, 3). One required treatment with aromatase inhibitor and tamoxifen, subsequently progressing

1 to true central puberty requiring addition of gonadotrophin-releasing hormone
2 analogue (Patient 2). Two had slowly progressing early puberty that did not require
3 treatment (Patient 1 at 7 years, 3 at age 6 years). One other male had no evidence of
4 early puberty but had bilateral macro-orchidism (Patient 5).

5 Six of the 7 men had testicular ultrasound, all with evidence of abnormalities,
6 the commonest being bilateral heterogeneous changes with lobulated appearance.
7 Five men have had testicular biopsy, three with normal biopsy and spermatogenesis
8 despite ultrasound changes. Patient 2 had biopsy evidence of Leydig cell hyperplasia
9 and normal spermatogenesis at age 19 years. Patient 3 had marked atrophy of germ
10 cells and Sertoli cells with evidence of absent spermatogenesis at age 14 years.
11 Biochemistry at age 18 years showed normal gonadotrophin levels: LH 1.2 U/L, FSH
12 5.7 U/L, testosterone 5.3 nmol/L, AMH 145.5 pmol/L (NR 3.57-160.7). Semen
13 analysis at age 24 revealed < 1 million sperm/ml.

14 *Gastrointestinal*

15 Eight individuals have had screening endoscopy, six with gastric and upper
16 gastrointestinal tract polyps with benign histology to date (Patients 2, 3, 4, 5, 7 and
17 16). Most had hamartomatous polyps histologically identical to those of Peutz Jegher
18 syndrome. Four of these had perioral freckles (Patients 2, 3, 7 and 8). Repeat
19 endoscopies over 2-7 years have not shown any new histological changes to date.
20 However, all have shown increase in number of polyps in the oesophagus, stomach
21 and duodenum.

22 Seven had multiple gall stones, including 4 men [patients 1-4, 7, 13, 15], five
23 requiring cholecystectomy. Hepatic abnormalities of non-alcoholic fatty liver disease
24 were found in 2, and two with hepatic cysts. Pancreatic cyst was seen in one patient
25 but significant underlying cardiorespiratory complications preclude biopsy or surgery
26 (Patient 5).

28 *Tumours*

29 GNAS positive myxoma was seen in two (Patient 9: hand, Patient 12: thigh).
30 Aggressive GNAS positive breast carcinoma was reported in one female (patient 14)
31 presenting age 41 years). She had no family history of breast carcinoma. Menstrual
32 cycles were normal prior to diagnosis of carcinoma. Her breast development started
33 at age 6-7 years with menarche at 9 years.

35 *Other health issues*

36 Four individuals (Patients 2, 3, 4 and 5) had evidence of high cardiac output
37 state, all >7 liters/metre²/min. with cardiac failure in 2 individuals (Patients 4 and 5)

1 including a man with restrictive lung disease, due to severe scoliosis requiring
2 nocturnal continuous positive airway pressure (5). He also requires home oxygen
3 intermittently. The condition is complicated by longstanding leukoerythroblastic
4 anaemia and massive splenomegaly. Patients 4 and 5 are treated with digoxin.
5 Patients 2 and 3 have a high output state without overt failure. No patient has
6 required treatment for hypertension.

7 Platelet dysfunction due to a platelet pool defect was reported in four of this
8 cohort (Patients 1, 3, 6, 14). Patient 6 had experienced catastrophic surgical blood
9 loss during orthopedic surgery prior to the use of platelet cover. Platelet cover during
10 later surgeries avoided excess bleeding. One patient with pan-ostotic FD had
11 splenomegaly and leuko-erythroblastic anemia presumed to be due to marrow
12 invasion by FD (Patient 5). Two patients developed type 2 diabetes mellitus (Patient
13 2 and 13), both of whom have GH excess with ongoing significantly elevated IGF-1
14 levels.

33 **DISCUSSION**

34 Whilst there have been numerous studies of larger numbers of adults with
35 MAS, they have focused on specific health outcomes. Our retrospective clinical
36 review of comprehensive health outcomes consists of the largest cohort of adult
37 patients with MAS with long term follow-up. We confirm reported experience of

continued worsening of severe craniofacial FD ¹⁴, particularly but not exclusively in the presence of GH excess and we identified endocrine hyper function (T3 toxicosis, GH excess) in 40% of our cohort, as with other studies ¹⁵. We also identified the GNAS gene mutation in one patient with aggressive breast cancer and two with a benign tumour ¹⁶.

Whilst gonadal pathology is increasingly recognized in males with MAS even without precocious puberty ⁵, our cohort included a male with marked germ and Sertoli cell atrophy and impaired spermatogenesis. These patients therefore require ongoing surveillance and management by adult clinicians familiar with these complex and interlinked clinical issues.

Comprehensive long term health outcome cohort reports in adults with MAS are few, although reviews of larger numbers are more common ¹⁷⁻¹⁹. An early report included 5 adults, assessed at median 47 years (24, 50). Endocrine hyper function and skeletal abnormalities were reported but other health outcomes were unknown ³. Another group of authors report their experience with 15 adults with MAS in a review article, although data was not systematically presented for those patients ⁴.

FD lesions in the appendicular skeleton of our cohort did not progress in adulthood, similar to reported experience, but continue to cause significant pain management issues. Due to recurrent fracture through FD lesions or radiologic reassessment by orthopaedic colleagues for hip, back, humeral and knee FD, we were able to review FD lesions and observe stability in appearance over many years. Repeated Technecium whole body scanning was not performed as considered only to be of value in identifying the original extent of lesions and not contributory to adult management. As adults do not increase size of the appendicular skeleton and bone turnover is much lower than children, major expansion of lesions is less likely in the absence of physical evidence of expanding appendicular skeletal lesions. Patients 4 and 5 have such severe scoliosis it is difficult to tell whether there might be change in extent of axial FD. Patient 13 has had multiple MR examinations at the site of thoracic vertebral FD without evidence of expansion and in keeping with long term pain control by bisphosphonate. However, recent spontaneous migration of long term intramedullary rods in the humeri of patients 2 and 5, through the distal end and through skin, have required replacement. The authors are not aware of other similar reports but this may become more common with time.

Bisphosphonate use in MAS has not been shown to reduce lesion size ²⁰ and is primarily for control of bone pain ²¹, utilized in three of our patients on a short term intermittent basis, similar to an adult cohort ²² Bisphosphonate was used in one of our patients who had a visual field defect due to optic canal compression by FD.

1 Stabilization of visual field defect for over 15 years was observed following 4 doses of
2 pamidronate. This is in keeping with current advice that surgical decompression
3 should only be used as a last resort if there is continued failing vision ²³. Newer
4 therapeutic options may offer hope, by altering the disease course via reduction of
5 lytic lesions in FD and MAS. Receptor activator of NF- κ B ligand (RANKL) is reported
6 to be over-expressed in FD cells ²⁴. A recent case report of a 9 year old boy with
7 severe FD and a rapidly expanding femoral lesion treated with Denosumab, a
8 humanized monoclonal antibody to RANKL, led to dramatic reduction of the
9 expanding lesion and bone pain ²⁵. There are no published reports of the use of
10 Denosumab in the context of visual disturbances due to optic canal compression due
11 to FD as far as we are aware.

12 Restrictive lung disease and cor pulmonale secondary to severe fibrous
13 dysplasia has been previously described in a twenty year old man ²⁶ and was seen in
14 two of our patients. A recent study in transgenic mice with long term activation of gsa
15 demonstrated changes in the bone marrow environment with bone marrow aplasia,
16 loss of haemopoietic stem cells and impaired megakaryocyte, erythrocyte
17 development ²⁷. Our study includes a patient with long standing leukoerythroblastic
18 anemia in association with MAS and panostotic FD, which we suggest could be
19 explained by marrow invasion by FD.

20 GH excess in our cohort was higher than that reported (13- 20%) in mixed
21 cohorts of pediatric and adult patients ^{3,18,19,28}. However in a report of 15 adults with
22 MAS, 8 (53%) developed GH excess ³. Our experience of treatment of GH excess in
23 MAS mirrors published evidence of difficulties in achieving biochemical normalization
24 with medical therapy ¹⁵. Pegvisomant, a GH receptor antagonist, has been shown to
25 be effective in a small number of patients with MAS and GH excess. ^{29,30} Cost
26 restricts current access in Australia. Pasireotide, a somatostatin analogue with
27 broader receptor binding profiles than other somatostatin analogues has been
28 reported to be effective in acromegaly ³¹. In our experience however, it caused
29 hyperglycemia that was impossible to control using > 3 units/kg/day of insulin, with
30 normalization of glucose after re-introduction of Octreotide. The increased risk of
31 diabetes with Pasireotide has been shown to be due to reduction in insulin levels and
32 incretin response without changes in insulin sensitivity ³²

33 Thyrotoxicosis frequency in our adult cohort is comparable to published
34 incidence of 11%-20%. ^{3,33}. The median age of presentation of published cases and
35 for our patients was in late childhood and early adolescence ^{3,33}, with implications for
36 transition. Early diagnosis and management is important as excess thyroid hormone

1 increases an already raised cardiac output further and contributes to risk for high
2 output cardiac failure.

3 Testicular abnormalities including macro-orchidism, ultrasound changes
4 including microlithiasis were common, as previously described ⁵. Unresolved issues
5 include threshold for testicular biopsy and ongoing monitoring, with recent guidelines
6 suggested ⁵. The impact of testicular lesions on fertility and its regulation in men with
7 MAS is currently unknown, requiring further study. None of our men have fathered
8 children to date but most testicular biopsies indicated normal spermatogenesis ,
9 despite case reports suggesting possibly impaired spermatogenesis in MAS ^{6,34}.
10 Only one of our cohort had marked atrophy of Sertoli cells on repeated testicular
11 biopsy with impaired spermatogenesis.

12 The Gsα protein is considered to be an oncogene. Transfection of
13 somatotrophs and thyroid cell lines with Gsα mutant lead to constitutive activation of
14 cAMP pathways and activated mitogenic signals ³⁵. It is thought that endocrine
15 and/or environmental factors may interact with genetic factors to influence the
16 neoplastic process. Our report includes a patient aged 42 years with a history of early
17 puberty, who developed grade 3 ductal carcinoma of the right breast, positive for
18 GNAS and estrogen receptor with no family history of breast cancer. Two previous
19 case reports of breast carcinoma in association with MAS did not have results of
20 GNAS mutation in the tumor^{9,36}. One of these also had GH excess and both had
21 precocious puberty, an independent risk for breast cancer.

22 Upper GIT polyps in MAS are increasingly recognized ¹¹. Given the
23 hamartomatous histology identical to that of Peutz Jegher syndrome in our cohort,
24 but the many other polyps recently catalogued, ongoing surveillance is essential. No
25 malignant changes have been seen to date. Peri- oral freckling was initially described
26 in 2011¹⁸ and recently confirmed in larger series ³⁷

27 The platelet defect in MAS is associated with increased platelet agonist
28 adenosine diphosphate (ADP) time with normal epinephrine response. Normal
29 platelet activation of ADP involves of GNAS inhibition and thus, the constitutionally
30 active Gsα protein in people with MAS has a direct role in platelet dysfunction ³⁸.
31 Platelet storage defects have potential to cause catastrophic surgical blood loss with
32 bleeding easily reduced by platelet transfusion at time of surgery or peri partum.
33 Evaluation of risk is mandatory for all MAS patients prior to major surgery, using
34 screening with PFA100 and latelet aggregometry.³⁷

35 **Conclusion**

36 In conclusion, our review of the spectrum of health outcomes in adults with
37 MAS demonstrates that increasingly severe consequences of extensive GNAS

1 affected tissue can occur. Adults who have MAS may have a higher risk for cancers
2 especially thyroid, breast, bone, gastrointestinal tumors and gonads. Ongoing
3 surveillance is required although risk is currently not defined. Endocrine hyper
4 function presents commonly in adolescents during the period of transition to adult
5 care, with major morbidity. Given the complexity and spectrum of health problems
6 encountered, multidisciplinary care of adults with MAS should include physicians
7 cognizant of potential new and evolving associated disorders.

9 **DECLARATION OF INTEREST**

10 The authors declare that there is no conflict of interest that could be perceived as
11 prejudicing the impartiality of the research reported.

13 **FUNDING**

14 This research did not receive any specific grant from any funding agency in the
15 public, commercial or not-for-profit sector.

17 **ACKNOWLEDGEMENT**

18 We would like to acknowledge the help of Lindy Tukavkin for assistance with data
19 collection.

26 **REFERENCES**

- 27 1. Zacharin M. Paediatric management of endocrine complications in McCune-
28 Albright syndrome. *Journal of pediatric endocrinology & metabolism : JPEM* 2005;
29 **18**(1): 33-41.
- 30 2. Zacharin M. The spectrum of McCune Albright syndrome. *Pediatric*
31 *endocrinology reviews : PER* 2007; **4 Suppl 4**: 412-8.
- 32 3. Lee PA, Van Dop C, Migeon CJ. McCune-Albright syndrome. Long-term
33 follow-up. *JAMA : the journal of the American Medical Association* 1986; **256**(21):
34 2980-4.
- 35 4. Chanson P, Salenave S, Orcel P. McCune-Albright syndrome in adulthood.
36 *Pediatric endocrinology reviews : PER* 2007; **4 Suppl 4**: 453-62.

- 1 5. Boyce AM, Chong WH, Shawker TH, et al. Characterization and management
2 of testicular pathology in McCune-Albright syndrome. *The Journal of clinical
3 endocrinology and metabolism* 2012; **97**(9): E1782-90.
- 4 6. De Luca F, Mitchell V, Wasniewska M, et al. Regulation of spermatogenesis
5 in McCune-Albright syndrome: lessons from a 15-year follow-up. *European journal of
6 endocrinology / European Federation of Endocrine Societies* 2008; **158**(6): 921-7.
- 7 7. Lala R, Andreo M, Pucci A, Matarazzo P. Persistent hyperestrogenism after
8 precocious puberty in young females with McCune-Albright syndrome. *Pediatric
9 endocrinology reviews : PER* 2007; **4 Suppl 4**: 423-8.
- 10 8. Collins MT, Sarlis NJ, Merino MJ, et al. Thyroid carcinoma in the McCune-
11 Albright syndrome: contributory role of activating Gs alpha mutations. *The Journal of
12 clinical endocrinology and metabolism* 2003; **88**(9): 4413-7.
- 13 9. Huston TL, Simmons RM. Ductal carcinoma in situ in a 27-year-old woman
14 with McCune-Albright syndrome. *The breast journal* 2004; **10**(5): 440-2.
- 15 10. de Araujo PI, Soares VY, Queiroz AL, dos Santos AM, Nascimento LA.
16 Sarcomatous transformation in the McCune-Albright syndrome. *Oral and
17 maxillofacial surgery* 2012; **16**(2): 217-20.
- 18 11. Zacharin M, Bajpai A, Chow CW, et al. Gastrointestinal polyps in McCune
19 Albright syndrome. *Journal of medical genetics* 2011; **48**(7): 458-61.
- 20 12. Wood LD, Noe M, Hackeng W, et al. Patients with McCune-Albright syndrome
21 have a broad spectrum of abnormalities in the gastrointestinal tract and pancreas.
22 *Virchows Arch* 2017.
- 23 13. Rivkees SA. Pediatric Graves' disease: management in the post-
24 propylthiouracil Era. *International journal of pediatric endocrinology* 2014; **2014**(1):
25 10.
- 26 14. Lee JS, FitzGibbon EJ, Chen YR, et al. Clinical guidelines for the
27 management of craniofacial fibrous dysplasia. *Orphanet journal of rare diseases*
28 2012; **7 Suppl 1**: S2.
- 29 15. Salenave S, Boyce AM, Collins MT, Chanson P. Acromegaly and McCune-
30 Albright syndrome. *The Journal of clinical endocrinology and metabolism* 2014;
31 **99**(6): 1955-69.
- 32 16. Delaney D, Diss TC, Presneau N, et al. GNAS1 mutations occur more
33 commonly than previously thought in intramuscular myxoma. *Modern pathology : an
34 official journal of the United States and Canadian Academy of Pathology, Inc* 2009;
35 **22**(5): 718-24.

- 1 17. Robinson C, Collins MT, Boyce AM. Fibrous Dysplasia/McCune-Albright
2 Syndrome: Clinical and Translational Perspectives. *Curr Osteoporos Rep* 2016;
3 **14**(5): 178-86.
- 4 18. Collins MT, Singer FR, Eugster E. McCune-Albright syndrome and the
5 extraskeletal manifestations of fibrous dysplasia. *Orphanet journal of rare diseases*
6 2012; **7 Suppl 1**: S4.
- 7 19. Boyce AM, Glover M, Kelly MH, et al. Optic neuropathy in McCune-Albright
8 syndrome: effects of early diagnosis and treatment of growth hormone excess. *The*
9 *Journal of clinical endocrinology and metabolism* 2013; **98**(1): E126-34.
- 10 20. Chan B, Zacharin M. Pamidronate treatment of polyostotic fibrous dysplasia:
11 failure to prevent expansion of dysplastic lesions during childhood. *Journal of*
12 *pediatric endocrinology & metabolism : JPEM* 2006; **19**(1): 75-80.
- 13 21. Chapurlat RD. Medical therapy in adults with fibrous dysplasia of bone.
14 *Journal of bone and mineral research : the official journal of the American Society for*
15 *Bone and Mineral Research* 2006; **21 Suppl 2**: P114-9.
- 16 22. Kelly MH, Brillante B, Collins MT. Pain in fibrous dysplasia of bone: age-
17 related changes and the anatomical distribution of skeletal lesions. *Osteoporosis*
18 *international : a journal established as result of cooperation between the European*
19 *Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA*
20 2008; **19**(1): 57-63.
- 21 23. Tan YC, Yu CC, Chang CN, Ma L, Chen YR. Optic nerve compression in
22 craniofacial fibrous dysplasia: the role and indications for decompression. *Plast*
23 *Reconstr Surg* 2007; **120**(7): 1957-62.
- 24 24. Piersanti S, Remoli C, Saggio I, et al. Transfer, analysis, and reversion of the
25 fibrous dysplasia cellular phenotype in human skeletal progenitors. *Journal of bone*
26 *and mineral research : the official journal of the American Society for Bone and*
27 *Mineral Research* 2010; **25**(5): 1103-16.
- 28 25. Boyce AM, Chong WH, Yao J, et al. Denosumab treatment for fibrous
29 dysplasia. *Journal of bone and mineral research : the official journal of the American*
30 *Society for Bone and Mineral Research* 2012; **27**(7): 1462-70.
- 31 26. Narayan RL, Maldjian PD. Restrictive lung disease and cor pulmonale
32 secondary to polyostotic fibrous dysplasia. *International journal of cardiology* 2009;
33 **131**(2): e48-50.
- 34 27. Schepers K, Hsiao EC, Garg T, Scott MJ, Passegue E. Activated Gs signaling
35 in osteoblastic cells alters the hematopoietic stem cell niche in mice. *Blood* 2012;
36 **120**(17): 3425-35.

- 1 28. Akintoye SO, Chebli C, Booher S, et al. Characterization of gsp-mediated
2 growth hormone excess in the context of McCune-Albright syndrome. *The Journal of*
3 *clinical endocrinology and metabolism* 2002; **87**(11): 5104-12.
- 4 29. Akintoye SO, Kelly MH, Brillante B, et al. Pegvisomant for the treatment of
5 gsp-mediated growth hormone excess in patients with McCune-Albright syndrome.
6 *The Journal of clinical endocrinology and metabolism* 2006; **91**(8): 2960-6.
- 7 30. Galland F, Kamenicky P, Affres H, et al. McCune-Albright syndrome and
8 acromegaly: effects of hypothalamopituitary radiotherapy and/or pegvisomant in
9 somatostatin analog-resistant patients. *The Journal of clinical endocrinology and*
10 *metabolism* 2006; **91**(12): 4957-61.
- 11 31. Petersenn S, Farrall AJ, Block C, et al. Long-term efficacy and safety of
12 subcutaneous pasireotide in acromegaly: results from an open-ended, multicenter,
13 Phase II extension study. *Pituitary* 2013.
- 14 32. Henry RR, Ciaraldi TP, Armstrong D, Burke P, Ligueros-Saylan M, Mudaliar
15 S. Hyperglycemia associated with pasireotide: results from a mechanistic study in
16 healthy volunteers. *The Journal of clinical endocrinology and metabolism* 2013;
17 **98**(8): 3446-53.
- 18 33. Tessaris D, Corrias A, Matarazzo P, et al. Thyroid abnormalities in children
19 and adolescents with McCune-Albright syndrome. *Hormone research in paediatrics*
20 2012; **78**(3): 151-7.
- 21 34. Benedict PH. Sex precocity and polyostotic fibrous dysplasia. Report of a
22 case in a boy with testicular biopsy. *American journal of diseases of children* 1966;
23 **111**(4): 426-9.
- 24 35. Ham J, Ivan M, Wynford-Thomas D, Scanlon MF. GH3 cells expressing
25 constitutively active Gs alpha (Q227L) show enhanced hormone secretion and
26 proliferation. *Mol Cell Endocrinol* 1997; **127**(1): 41-7.
- 27 36. Tanabeu Y, Nakahara S, Mitsuyama S, Ono M, Toyoshima S. Breast Cancer
28 in a Patient with McCune-Albright Syndrome. *Breast cancer* 1998; **5**(2): 175-8.
- 29 37. Pichard DC, Boyce AM, Collins MT, Cowen EW. Oral pigmentation in
30 McCune-Albright syndrome. *JAMA Dermatol* 2014; **150**(7): 760-3.
- 31 38. Bajpai A, Greenway A, Zacharin M. Platelet dysfunction and increased
32 bleeding tendency in McCune-Albright syndrome. *The Journal of pediatrics* 2008;
33 **153**(2): 287-9.
- 34

Patient ID	Sex	Age (years)	Age diagnosis (years)	Presenting feature leading to diagnosis	Café au lait	GNAS mutation +ve
1	M	22	17	Fracture femur	+	ND
2	M	24	2	Fracture femur	+	+
3	M	25	3	Fracture femur	+	+
4	M	28	4	Fracture femur	+	+
5	M	32	0.1	Large cafe au lait at birth	+	+
6	M	34	14	Fracture humerus	+	ND
7	M	39	5	Fracture femur	+	+
8	F	28	12	Fracture femur	+	ND
9	F	30	4	Mass in right ovary , precocious puberty	+	ND
10	F	31	5	Precocious puberty	+	ND
11	F	31	4	Precocious puberty	+	ND
12	F	38	7	Myxoma thigh	+	+

13	F	42	36	Pituitary tumour	+	+
14	F	45	18	Fracture femur	-	+
15	F	48	17	Painful hips	+	ND
16	F	49	28	Frontal bossing	+	+

Table 1: General characteristics, presenting feature and genetic diagnosis in adults with McCune Albright Syndrome

M: male; F: female; +: yes; -: no; ND: not done

Patient ID	FD	Craniofacial FD	Mobility aids	Phosphate treatment	BP> 18 years	History of early puberty	Treatment for early puberty	Testicular ultrasound	Testicular biopsy
1	Polyostotic	+	-	-	-	+	-	Heterogeneous changes	ND
2	Panostotic	+	+++	+	-	+	+	Heterogeneous changes Echogenic lesions Microlithiasis	Leydig cell hyperplasia Normal spermatogenesis Rpt biopsy no change
3	Panostotic	+	++	-	-	+	-	Echogenic lesions Microlithiasis	Marked atrophy Absent spermatogenesis
4	Polyostotic	+	+++	-	-	-	-	Microlithiasis	Normal biopsy Normal spermatogenesis
5	Panostotic	+	+++	+	+	-	-	Bilateral macro-orchidism Heterogeneous changes	Normal biopsy Normal spermatogenesis
6	Panostotic	+	-	-	-	-	-	ND	ND
7	Polyostotic	+	+	+	-	-	-	Heterogeneous changes	Normal biopsy Normal spermatogenesis
8	Polyostotic	-	-	-	-	-	-	NA	NA
9	Polyostotic	+	-	-	-	+	-	NA	NA
10	Polyostotic	+	-	-	+	+	-	NA	NA
11	Monosototic	+	-	-	-	+	+	NA	NA

12	Polyostotic	-	-	-	-	+	-	NA	NA
13	Polyostotic	+	-	-	+	+	-	NA	NA
14	Polyostotic	-	-	-	+	+	-	NA	NA
15	Polyostotic	-	+	-	-	-	-	NA	NA
16	Polyostotic	+	-	-	+	+	-	NA	NA

Table 2: Skeletal involvement and gonadal abnormalities in adults with McCune Albright Syndrome

FD: fibrous dysplasia; BP: bisphosphonate; ND: not done; NA: not applicable; +: yes; -: no;

Explanation for mobility aids +: crutches only; ++: crutches and wheelchair; +++: crutches, wheelchair and family assistance

Patient ID	T3 toxicosis	Thyroid ultrasound	GH excess (GH to OGTT, IGF1 SDS , prolactin)	Pituitary MRI	GI polyps	Hepatobiliary	High output state >7-8l/min	Others
1	+	Hot nodule Hyper and hypoechoic lesions	+	ND (CT normal)	-	Gallstone (cholecystectomy)	-	Platelet dysfunction
2	+	Hot nodule and hypoechoic lesions	+	Normal	+	Gallstone (cholecystectomy)	+	T2DM
3	+	MNG, hypoechoic lesions, microcalcification	+	Microadenoma 4 mm	+	Gallstones (cholecystectomy), NAFLD	+	Platelet dysfunction
4	-	Normal	Normal GH and IGF1	ND	+	Gallstones(cholecystectomy),	+	-
5	+	Hot nodule	+	Normal	+	Pancreatic cyst	+	Hypertension, restrictive lung disease , leukoerythroblastic anaemia Platelet dysfunction
6	-	ND	Normal GH, IGF1	ND	ND	ND	-	-
7	-	ND	+	Normal	+	Gall stones, gallbladder polyp, hepatic cyst	-	Hypertension
8	-	Nodules	Normal GH, IGF1	ND	ND	ND	-	-
9	-	Normal	Normal GH, IGF1	ND	ND	Normal	-	Myxoma hand , ovarian cyst
10	-	MNG	Normal GH, IGF1	ND	ND	Normal	-	-
11	-	ND	Normal GH, IGF1	ND	ND	ND	-	-
12	-	ND	Normal GH, IGF1	ND	ND	ND	-	Myxoma thigh
13	+	MNG	+	Pituitary tumour	ND	Gallstone (cholecystectomy), NAFLD, hepatic cyst	-	Hypertension, T2DM
14	-	ND	Normal GH and IGF1	ND	ND	Normal	-	Platelet dysfunction, breast

								carcinoma
15	-	MNG	Normal GH and IGF1	ND	-	Gall stones(cholecystectomy)	-	-
16	-	Nodules	Normal IGF1 -	ND	+	Hepatic cyst	-	-

Table 3: Thyroid abnormalites, growth hormone excess and other health problems in adults with McCune Albright Syndrome

GH: growth hormone; IGF-1: insulin like growth factor-1; SDS: standard deviation score; MRI: magnetic resonance imaging; GI: gastrointestinal; l/min: litres per minute; MNG: multinodular goitre, mU/L: millitunit per litre; NAFLD: non-alcoholic fatty liver disease; CCF: congestive cardiac failure; T2DM: type 2 diabetes mellitus; ND: not done; +: yes; -: no

Minerva Access is the Institutional Repository of The University of Melbourne

Author/s:

Wong, SC;Zacharin, M

Title:

Long-term health outcomes of adults with McCune-Albright syndrome

Date:

2017-11-01

Citation:

Wong, S. C. & Zacharin, M. (2017). Long-term health outcomes of adults with McCune-Albright syndrome. CLINICAL ENDOCRINOLOGY, 87 (5), pp.627-634. <https://doi.org/10.1111/cen.13419>.

Persistent Link:

<http://hdl.handle.net/11343/293293>