Long Term Health Outcomes Of Adults With McCune Albright Syndrome

Short running title: Adults with McCune Albright Syndrome

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Key words: Bisphosphonate, café au lait, cancer, fertility, fibrous dysplasia, gastrointestinal polyps, growth hormone excess, platelet dysfunction, thyrotoxicosis,
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 café 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, adult focus shifts to challenging problems of endocrine hyper function especially acromegaly and
thyrotoxicosis.\textsuperscript{3,4} Even though appendicular fibrous dysplasia usually stabilizes by late adolescence, adults with MAS often suffer significant pain and poor mobility due to existing lesions, together with worsening skull deformity, aggravated by acromegaly. In addition, endocrine hyperfunction and other health problems may also complicate overall skeletal management.

Emerging evidence suggests that gonadal abnormalities in men and women may affect fertility\textsuperscript{5-7}. Thyroid cancer\textsuperscript{8}, breast carcinoma\textsuperscript{9} and malignant sarcoma\textsuperscript{10} have been reported in MAS. There may also be a risk of gonadal\textsuperscript{5} and gastrointestinal tumors\textsuperscript{11,12}, with various types of gastrointestinal polyps reported in MAS\textsuperscript{11,12}. It is therefore imperative that clinicians providing adult care to these patients are aware of the spectrum of these problems. There are few reports of comprehensive long term outcomes and evolving health problems of adults with MAS.

SUBJECTS AND METHODS

A retrospective case note review was conducted for adults with MAS (aged $\geq$ 18 years) to report long term comprehensive health outcome in adulthood, regarding fibrous dysplasia, thyroid abnormalities, growth hormone (GH) excess, testicular abnormalities and other lesions known to be associated with the underlying condition. Case records of the private practice of one of the authors (MZ) were used to obtain this information. The majority were also previously managed by the same clinician during paediatric care. All investigations included were conducted as part of clinical monitoring of the patients. As we utilized data collected in routine clinical practice, ethical approval was not required. This report of clinical experience of long term adult outcome of MAS is unique in that these patients were managed by one single 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
extremely high in all, due to limited access incurred by facio-mandibular FD. Platelet cover prevented catastrophic blood loss in patient 1. 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 and only recently observed.

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

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

Growth hormone excess

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

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

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

Gastrointestinal

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

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

Tumours

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

Other health issues

Four individuals (Patients 2, 3, 4 and 5) had evidence of high cardiac output state, all >7 liters/metre²/min. with cardiac failure in 2 individuals (Patients 4 and 5).
including a man with restrictive lung disease, due to severe scoliosis requiring nocturnal continuous positive airway pressure (5). He also requires home oxygen intermittently. The condition is complicated by longstanding leukoerythroblastic anaemia and massive splenomegaly. Patients 4 and 5 are treated with digoxin. Patients 2 and 3 have a high output state without overt failure. No patient has required treatment for hypertension.

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

DISCUSSION

Whilst there have been numerous studies of larger numbers of adults with MAS, they have focused on specific health outcomes. Our retrospective clinical review of comprehensive health outcomes consists of the largest cohort of adult patients with MAS with long term follow-up. We confirm reported experience of
continued worsening of severe craniofacial FD \textsuperscript{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 \textsuperscript{15}. We also identified the
GNAS gene mutation in one patient with aggressive breast cancer and two with a
benign tumour \textsuperscript{16}.

Whilst gonadal pathology is increasingly recognized in males with MAS even
without precocious puberty \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{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 \textsuperscript{20} and
is primarily for control of bone pain \textsuperscript{21}, utilized in three of our patients on a short term
intermittent basis, similar to an adult cohort \textsuperscript{22} Bisphosphonate was used in one of
our patients who had a visual field defect due to optic canal compression by FD.

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

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

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

Thyrotoxicosis frequency in our adult cohort is comparable to published incidence of 11%-20%. The median age of presentation of published cases and for our patients was in late childhood and early adolescence, with implications for transition. Early diagnosis and management is important as excess thyroid hormone...
increases an already raised cardiac output further and contributes to risk for high output cardiac failure.

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

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

Upper GIT polyps in MAS are increasingly recognized. Given the hamartomatous histology identical to that of Peutz Jegher syndrome in our cohort, but the many other polyps recently catalogued, ongoing surveillance is essential. No malignant changes have been seen to date. Perioral freckling was initially described in 2011 and recently confirmed in larger series.

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

**Conclusion**

In conclusion, our review of the spectrum of health outcomes in adults with MAS demonstrates that increasingly severe consequences of extensive GNAS
affected tissue can occur. Adults who have MAS may have a higher risk for cancers especially thyroid, breast, bone, gastrointestinal tumors and gonads. Ongoing surveillance is required although risk is currently not defined. Endocrine hyperfunction presents commonly in adolescents during the period of transition to adult care, with major morbidity. Given the complexity and spectrum of health problems encountered, multidisciplinary care of adults with MAS should include physicians cognizant of potential new and evolving associated disorders.

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

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REFERENCES


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

M: male; F: female; +: yes; -: no; ND: not done
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</table>

### 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
<table>
<thead>
<tr>
<th>Patient ID</th>
<th>T3 toxicosis</th>
<th>Thyroid ultrasound</th>
<th>GH excess (GH to OGTT, IGF1 SDS, prolactin)</th>
<th>Pituitary MRI</th>
<th>GI polyps</th>
<th>Hepatobiliary</th>
<th>High output state &gt;7-8l/min</th>
<th>Others</th>
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<tbody>
<tr>
<td>1</td>
<td>+</td>
<td>Hot nodule</td>
<td>(GH 54 mU/L, IGF1 SDS 0.0, prolactin 320 mU/L)</td>
<td>ND</td>
<td>-</td>
<td>Gallstone (cholecystectomy)</td>
<td>-</td>
<td>Platelet dysfunction</td>
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<tr>
<td>2</td>
<td>+</td>
<td>Hot nodule and hypoechoic lesions</td>
<td>(GH 100 mU/L, IGF1 SDS +2.0, prolactin 527 mU/L)</td>
<td>Normal</td>
<td>+</td>
<td>Gallstone (cholecystectomy), recurrent</td>
<td>+</td>
<td>T2DM</td>
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<tr>
<td>3</td>
<td>+</td>
<td>MNG, hypoechoic lesions, microcalcification</td>
<td>(GH 38 mU/L, IGF1 SDS +2.0, prolactin 424 mU/L)</td>
<td>Microadenoma 4 mm</td>
<td>+</td>
<td>Gallstones (cholecystectomy), NAFLD</td>
<td>+</td>
<td>Platelet dysfunction</td>
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<td>Normal GH and IGF1</td>
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<td>Gallstones (cholecystectomy),</td>
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<td>(GH 109 mU/L, IGF1 SDS +1.0)</td>
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<td>Pancreatic cyst</td>
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<td>Normal GH, IGF1</td>
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<td>ND</td>
<td>Normal</td>
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<td>Myxoma hand, ovarian cyst</td>
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<td>ND</td>
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<tr>
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<td>ND</td>
<td>Normal GH, IGF1</td>
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<td>ND</td>
<td>-</td>
<td>Myxoma thigh</td>
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<td>+</td>
<td>MNG</td>
<td>(GH 16 mU/L, IGF1 SDS +4.5, prolactin 94mU/L)</td>
<td>Pituitary tumour</td>
<td>ND</td>
<td>Gallstone (cholecystectomy), NAFLD, hepatic cyst</td>
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<td>Hypertension, T2DM</td>
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<tr>
<td>14</td>
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<td>ND</td>
<td>Normal GH and IGF1</td>
<td>ND</td>
<td>ND</td>
<td>Normal</td>
<td>-</td>
<td>Platelet dysfunction, breast</td>
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Table 3: Thyroid abnormalities, growth hormone excess and other health problems in adults with McCune Albright Syndrome

<table>
<thead>
<tr>
<th>No</th>
<th>Lesion</th>
<th>GH Status</th>
<th>IGF-1 Status</th>
<th>SDS</th>
<th>MRI</th>
<th>GI</th>
<th>GI Status</th>
<th>Other Findings</th>
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<td>MNG</td>
<td>Normal GH and IGF1</td>
<td>ND</td>
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<td>Gall stones (cholecystectomy)</td>
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<tr>
<td>16</td>
<td>-</td>
<td>Nodules</td>
<td>Normal IGF1</td>
<td>ND</td>
<td>+</td>
<td>Hepatic cyst</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>

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: milliunit per litre; NAFLD: non-alcoholic fatty liver disease; CCF: congestive cardiac failure; T2DM: type 2 diabetes mellitus; ND: not done; +: yes; -: no
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Author/s:
Wong, SC; Zacharin, M

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Date:
2017-11-01

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