

McCune Albright Syndrome: Case Report and Review of Literature

Nunilo I. Rubio Jr^a, Shahla Nader^b, Patrick G. Brosnan^c

^aDepartment of Pediatrics, ^bDepartment of Internal Medicine, ^cDepartment of Pediatrics, ^cUniversity of Texas at Houston, USA

MMcCune-Albright syndrome is a rare disease defined by two of the three classical findings of polyostotic fibrous dysplasia, café au lait spots, and endocrine abnormalities, the most common being precocious puberty. This disease manifests in a mosaic pattern, signifying the sporadic development of disease during embryogenesis. Recent literature has characterized the pathogenesis of this disease, which results from a mutation in the GNAS gene that causes a persistent activation of the G stimulatory-alpha subunit of the G protein cellular signaling complex. This causes a 'gain of function' in the cells affected. This paper describes three cases of McCune Albright's syndrome and reviews the recent literature regarding the pathogenesis of each of the classical findings.

Keywords: Mc-Cune Albright, café au lait spot, precocious puberty, polyostotic fibrous dysplasia, G stimulatory-alpha mutation

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Introduction

McCune-Albright syndrome was first described in 1936 as the triad of café au lait spots of the skin, polyostotic fibrous dysplasia, and multiple endocrine abnormalities in-

cluding precocious puberty^{1, 2} (Fig.1-3). The diagnosis is generally accepted if 2 of the 3 symptoms are present because of the wide spectrum of disease phenotypes^{3,4}. These 3 cases illustrate the variability of presentation of this disease.

Case 1

An 11 year old Hispanic boy who attended from Mexico presented for evaluation of multiple fractures. He was the product of a fraternal twin gestation and reportedly had no

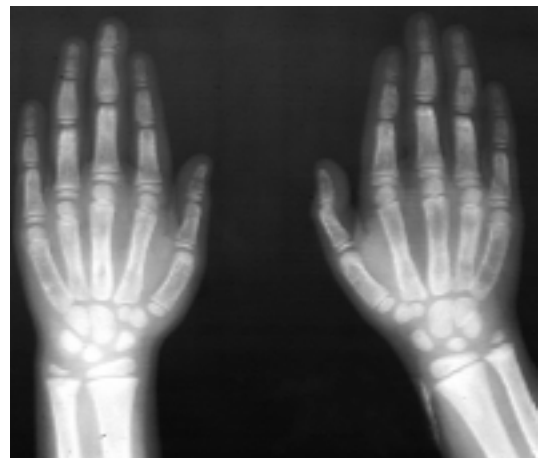


Figure 1a. Bony dysplasia: expansive sclerotic texture of metacarpals and digits with ground-glass appearance.

Correspondence: Nunilo I. Rubio Jr., University of Texas at Houston, Department of Pediatrics, 6431 Fannin, Suite 3.122, Houston, Texas 77030
E-mail: nunilo.i.rubio@uth.tmc.edu



Fig. 1b. Bony dysplasia



Fig. 1c. Bony dysplasia

problems up until age two, when he developed his first fracture. Subsequently, he sustained other multiple fractures throughout his childhood involving his legs and upper arm.

On physical exam, he was found to have several bony deformities, including a right posterior ribcage deformity and a marked valgus alignment of both lower extremities. He also was noted to have 'soft' teeth which crumbled and occasionally fell out. Café au lait spots were visible on the nape of the neck, right buttock, and posterior thigh. In particular, he was noted to have a hyperpigmented spot with irregular borders in the middle of his lower back. His testes, on initial examination, were 10 milliliters each with Tanner I stage pubic hair. Radiographs of his bones showed generalized polyostotic involvement, more on the left than the right side. Initial laboratory tests included normal thyroid function tests, calcium, and intact parathyroid hormone. Later in the course of his disease, he developed a phenocopy of x-linked hypophosphatemic rickets. He was initially treated with phosphate and calcitriol replacement and was later given the bisphosphonate pamidronate secondary to excessive bone turnover indicated by elevation of urine N-telopeptide, a marker for osteoclastic resorption, and of osteocalcin, a marker of bone formation (Table 1).

Case 2

The case was first seen at 2 years and 4 months of age for evaluation of leg/arm length discrepancy. She was born at term without complications, but at one month of age was found to have discoloration of the upper and lower right extremities and trunk. At five months of age, she was found to have a shorter right arm and leg versus her left extremities. Her developmental milestones were normal. On physical exam, she was found to have a 3 centimeter leg length discrepancy and a 1.5 centimeter arm length discrepancy. She was also noted to have hyperpigmentation of the trunk, upper extremities and lower extremities with predominance on the right side. Radiographic studies confirmed a 4.2 centimeter leg length discrepancy as well as polyostotic fibrous dysplasia consistent with McCune Albright syndrome. Laboratory tests included a normal calcium, phosphorus, and thyroid function (Table 1).

Table 1. Laboratory findings in two cases of McCune Albright syndrome

Case 1:	Normal range
Calcium 9.1 mg/dL	8 -11 mg/dL
Normalized calcium 5.04 mg/dL	4.6-5.2mg/dL
Phosphorus 2.1mg/dL	2.5-5 mg/dL
Alkaline phosphatase 1893 IU/L	135-530 IU/L
Creatinine 0.5 mg/dL	0.2-1.4mg/dL
Urine calcium/creatinine ratio: 0.01	0-0.3, (u cr 182.3 mg/dl, u ca 1.6 mg/dL)
Intact PTH 59 pg/mL	10-65 mg/dL
Serum cortisol 10.9 µg/dL	PM: 2-9 ug/dL
Adrenocorticotrophic hormone (ACTH) 15 pg/mL	0-60 pg/mL
Thyroid stimulating hormone (TSH) 1.09 µIU/mL	0.32-5 uIU/mL
Total thyroxine (T4) 7.2 ug/mL	4.5-12.5 ug/mL
Insulin-like growth factor-1 (IGF-1) 97 ng/mL	180-440 ng/mL
Testosterone 20 ng/dL	3-10ng/dL
Tmp/gfr = 3.0	(Normal)
(U phos 13.5 mg/dL x 0.4 Cr/ (phos 2.4 x 68.1 mg/dL uCr))	
Prior to pamidronate therapy:	
Osteocalcin 62.9 ng/mL	1.1-10.8ng/mL
N-telopeptide 644 nmoles BCE/mmol creatinine	10-65 nmol BCE/mmol creatinine
Renal ultrasound was normal.	
Case 2:	
Birth history: Pregnancy uncomplicated, spontaneous vaginal delivery. No reported problems.	
Calcium 10.2 mg/dL	8.5-11 mg/dL
Phosphorus 4.8 mg/dL	4-8 mg/dL)
Thyroid stimulating hormone (TSH) 1.3 µIU/mL	0.4-10 µIU/mL
Total thyroxine (total T4) 8.2 µg/dL	4.5-12.5 µg/dL
Follicle stimulating hormone (FSH) 5 mIU/mL	2.5-16 mIU/mL premenopausal
Calcium 9.5 mg/dL	8.5-10.5 mg/dL
Phosphorus 5.3 mg/dL	3.5-6.0 mg/dL

Case 3

This patient was transferred to our institution at 2 weeks of age for persistent jaundice. He was found to have mildly elevated direct and indirect bilirubin, hypoalbuminemia, and moderately elevated transaminases. The baby also had persistent tachycardia, mild congestive heart failure, and significantly elevated free thyroxine levels with suppressed thyroid stimulating hormone. Thyroid stimulatory antibodies were absent. On examination, he was found to have faint brown pigmentation with ragged edges on his back and right leg. Hyperthyroidism was initially controlled with

propylthiouracil, Lugol's solution, and propranolol. But after four months, the patient developed rash and thrombocytopenia. He became severely hyperthyroid upon withdrawal of the propylthiouracil and was given radioiodine, resulting in permanent hypothyroidism subsequently controlled with levothyroxine replacement.

Around the time of admission, the patient was also found to have nephrocalcinosis on plain radiographs and ultrasound along with greatly decreased bone density with an unsuspected fracture. He was persistently hypercalcemic and hypercalciuric with appro-

priately suppressed parathyroid hormone. A course of pamidronate would lower the calcium and end hypocalcemia for about 6 to 8 weeks. But during his nine months of life, the patient had nine fractures from gentle handling.

The patient had cortisol levels which were persistently at, or above, the upper limit of normal and had elevated 24 hour urinary cortisol/creatinine ratios with suppressed adrenocorticotropic hormone (ACTH). Despite the evidence suggesting the hypercortisolism, adrenalectomy was not attempted.

At 9 months of age, the patient had two brief episodes of unexplained high fever and tachyarrhythmia and died following the second such episode. On postmortem the patient had evidence of myocardial infarction and had atrophy of most of the adrenal cortex, believed to be caused by clonal hyperfunction of the remaining cells.



Figure 2. Café au lait spots in McCune Albright Syndrome



Figure 3. Precocious puberty in McCune Albright Syndrome

Discussion

The etiology of McCune Albright's syndrome is a defect in the G stimulatory-alpha (Gs-alpha) component of the G-protein signaling pathway of the cell membrane.⁵⁻⁹ Normally, in its inactive state, the G-protein complex is located on the inner cell membrane and is comprised of a guanosine diphosphate-bound alpha subunit attached to a beta and gamma subunit. This complex is linked to a 7 transmembrane domain receptor, and when a ligand attaches to this receptor, the exchange of guanosine diphosphate (GDP) for guanosine triphosphate (GTP) on the alpha subunit is facilitated. The newly formed GTP-alpha subunit complex then dissociates from the beta/gamma components and activates an effector, in this case the neighboring adenylyl cyclase transmembrane protein which, in turn, catalyzes the production of cyclic adenosine monophosphate (AMP) from adenosine triphosphate (ATP).¹⁰ The cyclic AMP initiates a cascade of cellular events ending in the production of hormonal end products or cellular activity. An intrinsic guanosine triphosphatase on the alpha subunit eventually hydrolyzes the GTP back

to GDP which then permits binding of the alpha subunit back to the beta/gamma subunit and reversion to its inactivated state.

In McCune-Albright patients, a somatic missense mutation on the alpha subunit is present, resulting in impaired guanosine triphosphatase activity which causes persistent adenylate cyclase activation and cellular hyperfunction. One of the major mutations described is a point mutation at position Arg201 on exon 8 of the G-stimulatory alpha gene (GNAS gene). Lumbroso et al in 2002 studied 80 patients with McCune-Albright syndrome for the prevalence of this mutation.¹⁰ Depending on the tissue studied, mutation analysis at the Arg201 site was positive in 7% to 85% of the cells. In 2004, Lumbroso et al had the opportunity to genotype 113 patients with McCune Albright syndrome and were able to detect the mutation in approximately 90% of the affected tissue.¹¹ This somatic mutation can be found in many organs, including pituitary, adrenal cortex, liver, thyroid, parathyroid, bone, ovary, testis, pancreas, intestine, spleen, skin fibroblasts, heart.^{6,8,9,12,13} It is believed that this mutation occurs as a post-zygotic event, resulting in a 'mosaic' presentation which accounts for the many phenotypic variations of this disease. Evidence for this mosaicism comes from the 'asymmetrical' bony and organ distribution as well as a hyperpigmentation distribution that follows the 'lines of Blaschko' or nevus lines.¹⁴ These represent the dorso-ventral outgrowths of separate populations of cells during embryogenesis.¹⁵ To date, there have been no reports of heritable McCune-Albright syndrome, strengthening the theory that the mutation is lethal to the zygote.¹⁶

One of the first characteristics of McCune Albright syndrome is osteitis fibrosa disseminata, a form of fibrous dysplasia. In general, fibrous dysplasia exists in three forms: monostotic (70% of cases), polyostotic (27% of cases), and polyostotic associated with café au lait spots and endocrine abnormalities, otherwise known as McCune Albright's syndrome, which accounts for only 3% of

cases with fibrous dysplasia.¹⁷ Osteogenic cells with the Gs-alpha defect remain activated which results in a loss of bony trabecular architecture and subsequent predisposition to fracture. Riminucci et al (1999) histopathologically examined the affected bone in McCune Albright's patients and described 3 common patterns - a 'Chinese writing' form, a 'Pagetoid' form, and a hypercellular form.¹⁸ In all of these lesions, a disordered bony architecture was noted. These lesions usually occur on one side of the body, again emphasizing the mosaic inheritance, and are often found during workup of fracture in children. Leet et al (2004) analyzed the incidence of fracture in McCune Albright's syndrome by age and site and found that the highest incidence of fracture occurred within the 6-10 year age range and most often in the femoral bone.¹⁹ These lesions of fibrous dysplasia rarely convert to malignancy but if they do, osteosarcoma or malignant fibrous histiocytoma may develop in the 3rd or 4th decade of life.⁹ The GNAS gene mutation is seen in the osteoblastic cell lines and in some patients can produce a hypophosphatemic osteomalacia at sites remote from the fibrous dysplasia. Riminucci et al in 2003 and more recently Yamamoto et al in 2005 demonstrated high levels of fibroblast growth factor 23 in these patients.^{20,21} This growth factor is a protein seen to be elevated in x-linked and autosomal dominant hypophosphatemic rickets and induces renal phosphate wasting, diminished 1-alpha hydroxylation of 25-hydroxy vitamin D in renal tubule cells, and inhibits bone matrix calcification. Treatment of extensive fibrous dysplasia includes bisphosphonates to block bone resorption and surgical resection of the bony dysplasia if necessary.²²⁻²⁴

Café au lait spots comprise another of the major hallmarks of this disease (although 10% of the normal population can have 1 to 5 lesions)^{1,2} In these patients, the café au lait spots can be faint at birth and often are missed, but as the patient gets older, the lesions gradually darken.^{25,26} One characteristic lesion in McCune Albright patients is the

'Coast of Maine' appearance of the café au lait spot which emphasizes the 'irregularity' of the borders of these lesions. Kim et al. in 1999 isolated the melanocytes, fibroblasts, and keratinocytes from these pigmented lesions and determined that the G stimulatory-alpha mutation was present solely in the melanocytes and not in the other two cell lines.²⁷ This mutation was eventually discovered to increase tyrosinase activity. Tyrosinase is a copper-binding transmembrane glycoprotein which catalyzes the hydroxylation of tyrosine, the first step towards melanin biosynthesis. Over time, the faint café au lait spots evolve to darker and more visible lesions due to the persistent accumulation of melanin via this mechanism.

The third hallmark of McCune Albright's disease is the involvement of the endocrine system, of which precocious puberty is the predominating and common initial presentation among affected girls.⁹ This early sexual development stems from the ability of the disease to create multiple hyperfunctioning ovarian cysts which form and regress spontaneously, producing large amounts of estradiol in the process.²⁸ The number and size of these cysts dictate the amount of estradiol synthesized.²⁹ It is important to remember that this is not a centrally mediated precocious puberty but rather a peripheral gonadal event caused by the autonomous functioning cysts.²⁸ It is a nonsustained pseudoprecocious state. Follicle stimulating hormone and luteinizing hormone levels remain in the prepubertal range. Therefore, suppression of gonadotropins with luteinizing hormone releasing hormone analog (LHRH analog) does not work except as an adjunct, when body mass increase eventually triggers central puberty. The precocious puberty may eventually lead to closure of the epiphyses and resultant short stature. It is interesting to note that although the total volume of the ovaries is equivalent to that of a woman with central puberty, there is a marked asymmetry of the individual ovarian sizes, often with only one ovary affected, giving further evidence for a 'mosaic'

inheritance.²⁸ Treatment involves direct blockade of sex steroid synthesis with ketoconazole, aromatase inhibitors (anastrozole, testolactone) and now possibly tamoxifen which not only diminishes the level of estrogen, but also decreases the size of the cysts.³⁰⁻

³⁴ In terms of reproduction, the patients are still fertile but vertical transmission of this mutation is lethal and results in a higher number of spontaneous abortions in this population. In men, testicular maturity occurs in variable degrees. It is estimated that only 10% of the McCune-Albright patients who manifest precocious puberty are males.⁹

Apart from precocious puberty, McCune Albright's syndrome can present in other endocrine systems as follows: Cushing's syndrome resulting from primary adrenal hyperplasia, non-antibody mediated primary hyperthyroidism/nodular adenomatous goiter, and pituitary adenomas, the more common being somatotropinomas and prolactinomas.^{8,12,35,36}

The incidence of these manifestations is variable. Thyroid disease is regarded as the second most common endocrine manifestation in McCune-Albright syndrome but reported rates vary from 2.6% (3 of 113 patients, Lumbroso et al, 2004) to 42% (8 of 19 patients, Feuillan et al, 1990).^{11,37} Ultrasound of the thyroid has also shown varied findings, ranging from a normal appearance to inhomogeneity of the gland and echogenic areas suggestive of thyroid nodule.³⁷ Adrenal disease is also a common manifestation – Lumbroso et al reported that 7 of 113 patients had hypercortisolism.¹¹ Growth hormone excess is also a common finding. Akintoye et al in 2002 studied 58 patients with McCune Albright syndrome and discovered 12 patients with growth hormone excess, giving a prevalence of 21% in his series.³⁵ Eleven of his twelve patients (92%) had concomitant elevations of prolactin. Magnetic resonance imaging of the pituitary showed adenomas in only 4 of 12 patients, all of which were less than 2.5 centimeters and did not invade the cavernous sinus.

Treatment is similar to the standard care for patients with these individual diseases.^{3,11,13} In the case of hyperthyroidism, antithyroid medications, radioactive iodine therapy, and surgery have been implemented.¹³ The adrenocorticotrophic-independent Cushing's syndrome has been treated with adrenalectomy.^{6,26} For excess growth hormone or prolactin production, surgery and radiation therapy have been tried with varying results.¹³ Medical therapy with somatostatin analogs may however be the treatment of choice as many times pituitary adenomas are not visualized. Even if a pituitary adenoma is visualized, fibrous dysplasia of the skull may hinder surgical approaches for pituitary adenoma resection.³⁵ Radiation therapy also carries a risk of sarcomatous transformation of the fibrous dysplasia.³⁵

Non-endocrine organs can also be affected by McCune Albright's syndrome. In the liver, it can produce nodular hyperplasia, biliary dysfunction, and in neonates can cause severe jaundice.⁶ Gastrointestinal polyps and hyperplasia of the spleen and pancreatic islet cells are other intestinal expressions of disease.^{6,8} In the heart, hypertrophic cardiac myocytes can be seen.⁸ Kidney involvement often presents with nephrocalcinosis but the etiology may be multifactorial. One plausible theory involves the previously described hypophosphatemic phenotype in these patients as evidenced by low phosphate and low tubular reabsorption of phosphate with high urinary phosphate levels. Microcephaly, devel-

opmental delay, and failure to thrive are also other manifestations of neonatal disease.⁶ Neonatal McCune Albright's syndrome is rare, but its presentation is more severe. Case reports have described severe neonatal Cushing's syndrome needing bilateral adrenalectomy for control, precocious puberty, liver dysfunction, and thyroid disease.^{6,38,39} Early death from myocardial dysfunction is very common in neonatal McCune Albright's syndrome.

Conclusion

In summary, McCune Albright's syndrome stems from a Gs-alpha mutation, resulting in a hyperstimulation effect in the affected cell lines. It is a sporadic somatic mutation during embryogenesis which then manifests in a mosaic fashion and explains the asymmetrical pattern of disease. Two of three characteristics are generally accepted for diagnosis of this syndrome. These include: café au lait spots which may be faint in early childhood but darken with age, osteitis fibrosa disseminata which can be seen in a mosaic pattern, and multiple endocrine abnormalities, the most common being precocious puberty. Therapy is aimed specifically at the affected organs.

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