

Rare association of schizophrenia and unilateral Graves' disease with contralateral thyroid hemigenesis in two cases of McCune-Albright syndrome

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ABSTRACT

The classical triad of McCune-Albright syndrome (MAS) consists of polyostotic fibrous dysplasia (FD), skin hyperpigmentation (café-au-lait spots), and endocrine dysfunction, frequently seen in females as precocious puberty. Etiology is genetically based and is explained by mosaicism of activating somatic mutations of the alpha-subunit of Gs protein. Clinical presentation is varied and is dependent on the particular distribution of affected cells, causing a broad spectrum of endocrine and non-endocrine manifestations. Typical endocrinopathies are precocious puberty, hyperthyroidism, growth hormone excess, hyperprolactemia, and hypercortisolism. Manifestations usually occur during infancy and childhood. We present 2 classical cases of MAS with rare association of cerebral and endocrine dysfunction (unilateral Graves' disease with contralateral thyroid hemigenesis). The first case is an adult onset MAS with hyperparathyroidism and schizophrenia; this association is hitherto unreported in literature. Literature search showed that mutations in the Gs α gene may be associated with the pathogenesis of schizophrenia which is similar to the underlying factor in MAS. The second is a child exhibiting classical MAS with hyperthyroidism (unilateral Graves' disease) which is common but is associated contralateral thyroid hemigenesis.

Key words: McCune Albright syndrome; Unilateral Graves' disease; Contralateral thyroid hemigenesis; Hyperparathyroidism; Schizophrenia

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INTRODUCTION

McCune-Albright syndrome (MAS) was first described in 1937 by Donovan James McCune and Fuller Albright [1, 2]. It is a genetic abnormality and comprises of polyostotic fibrous dysplasia (FD), café-au-lait spots, and endocrine dysfunction like precocious puberty, hyperthyroidism, growth hormone excess, hyperprolactemia, and hypercortisolism. Precocious puberty is the most common endocrine feature in MAS and is the result of gonadotropin-independent autonomous ovarian or testicular dysfunction. A post-zygotic mutation of the gene *GNAS1* (Guanine Nucleotide binding protein, Alpha Stimulating activity polypeptide 1), on the long (q) arm of chromosome 20 at position 13.3 is implicated in MAS.

CASE 1

We present a 17 year old girl with precocious puberty, Café au lait spot over left arm, left jaw, right forearm and right tibia along with FD. In view of hypercalcemia and high parathormone values patient was referred for a whole body bone scan to look for metabolic bone disease. On careful interrogation, patient was found to have social isolation, cognitive disorder, emotional blunting and hallucinations (visual and aural). Patient was referred to a psychologist who clinically confirmed presence of schizophrenia. Clinically patient also exhibited brachydactyly and bulbous terminal phalanges. Such a constellation of MAS, hyperparathyroidism and schizophrenia is hitherto unreported. ^{99m}Tc MDP bone scan (Figure 1) showed fibrous dysplasia of skull bones, mandible on left side, with 'superscan appearance' (faintly visualised kidneys). Multiple brown tumours characteristic of hyperparathyroidism were identified on bone scan and are found in proximal shaft of right ulna and right tibia (thin arrow). 'Osteitis fibrosa cystica' was also noted which are evident as hot spots in bilateral terminal phalanges of hands (bold arrow).

Multiple brown tumours were seen in proximal shaft of right ulna and right tibia characteristic of hyperparathyroidism. Hot spots in bilateral (bulbous) terminal phalanges of hands termed as 'Osteitis fibrosa cystica' was also noted. ^{99m}Tc -SestaMIBI dual phase parathyroid scintigraphy (Figure 2a) confirmed a large left inferior parathyroid adenoma. Multidetector computed tomography (MDCT, Figure 2b) of skull showed an expansile lytic lesion (6.2 x 2.7 cm) with soft tissue component involving the body of left mandible and symphysis menti with lytic, sclerotic lesions involving craniofacial bones suggesting fibrous dysplasia. FD was histologically confirmed. Left inferior parathyroidectomy was performed and histology (Figure 2c) was consistent with an atypical parathyroid adenoma. Apart from hydrocephalus, cerebral manifestations of MAS are unknown. Literature search showed that mutations in the *Goa* gene may be associated with the pathogenesis of schizophrenia which is similar to the underlying factor in MAS [3, 4].

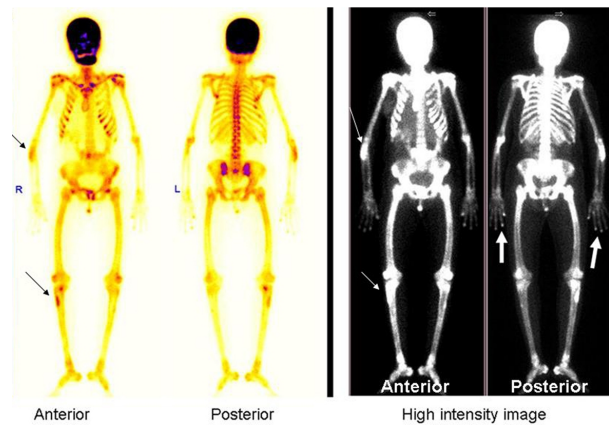


Fig 1. ^{99m}Tc MDP whole body bone scan showed fibrous dysplasia of skull bones, mandible on left side, with 'superscan appearance' (faintly visualised kidneys). Multiple brown tumors characteristic of hyperparathyroidism were identified on bone scan and are found in proximal shaft of right ulna and right tibia (thin arrow). 'Osteitis fibrosa cystica' was also noted which are evident as hot spots in bilateral terminal phalanges of hands (bold arrow).

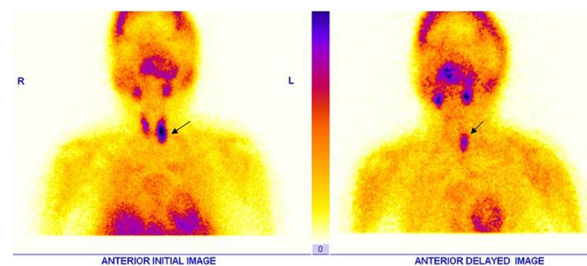


Fig 2a. ^{99m}Tc -SestaMIBI dual phase parathyroid scintigraphy: Initial image shows normal tracer uptake in both lobes of thyroid gland with focal increased tracer uptake at left inferior parathyroid gland region. Delayed image shows focal abnormal tracer retention at the above site with complete washout of tracer from rest of thyroid gland confirming a classical left inferior parathyroid adenoma (arrow).



Fig 2b. Multidetector computed tomography (MDCT) of skull showed an expansile lytic lesion (6.2 x 2.7 cm) with soft tissue component involving the body of left mandible and symphysis menti suggesting fibrous dysplasia.

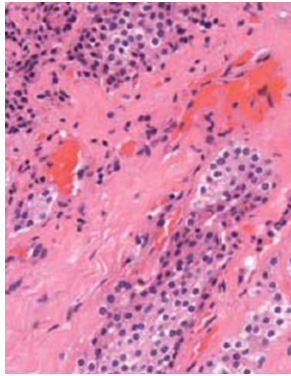


Fig 2c. Histological section of left inferior parathyroidectomy was consistent with an atypical parathyroid adenoma.

CASE 2

A 4 year old female child presented with breast enlargement, vaginal bleeding and palpitations. Biochemically patient had an autonomous ovarian hyperfunction. Abdominal ultrasound showed pubertal uterus with epithelial thickness of 8mm. Clinically, patient had tachycardia, café au lait spots with midline limitation. Free T4 was 1.9 ng (upper limit 1.7) and TSH was 0.001 uIU/ml. Patient was referred for a skeletal scintigraphy to look for any fibrous dysplasia as part of MAS workup. Due to suspected hyperthyroidism a $^{99m}\text{TcO}_4$ thyroid scintigraphy was also requested.

^{99m}Tc MDP whole body bone scan (Figure 3) showed polyostotic fibrous dysplasia [5] of bilateral parietal, right humerus, right radius and suspicious in L2 and L3 vertebrae.

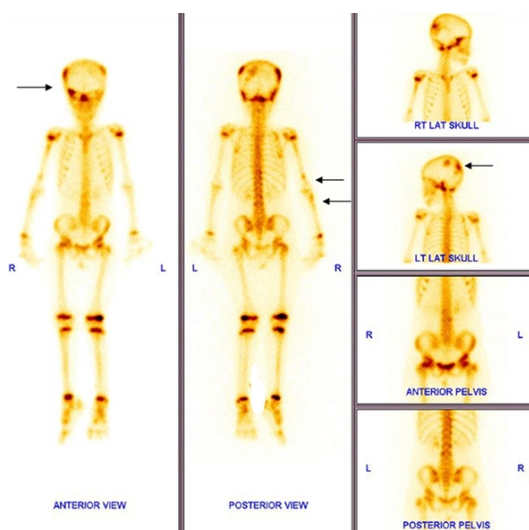


Fig 3. Bone scan showed polyostotic fibrous dysplasia of bilateral parietal, right humerus, greater wing of right sphenoid and skull base, right radius and suspicious lesions in L2 and L3 vertebrae.



Fig 4. ^{99m}Tc thyroid scan revealed absence of left lobe of thyroid gland. Right lobe of thyroid gland is enlarged with increased trapping function suggesting unilateral Graves' disease and a suspicious rudimentary pyramidal lobe.

Thyroid scintigraphy (Figure 4) revealed non visualization of left lobe of thyroid gland. Right lobe of thyroid gland appears enlarged with increased trapping function indicating unilateral Graves' disease with a suspicious pyramidal lobe. Ultrasound of neck confirmed above findings. Literature review shows the left lobe to be absent in 80% of cases [6]. Fibrous dysplasia in MAS can involve any bone but most commonly affects the long bones, ribs, and skull. It varies in severity and extent. Patient was prescribed Tab Tamoxifen 10mg once daily, letrozole and Neomercazole 5 mg once daily. Patient is showing clinical improvement at 6 months follow-up.

DISCUSSION

Research shows that the G protein/cAMP/adenylate cyclase signaling pathway is clearly implicated in the multiorgan involvement of MAS. Mutations in the regulatory G α protein (encoded by the GNAS gene) were the underlying molecular etiology of MAS [3, 4]. The hormones MSH (melanocyte stimulating hormone), LH (luteinizing hormone), TSH (thyroid stimulating hormone), GHRH (growth hormone stimulating hormone), and ACTH (adrenocortical stimulating hormone) all signal through the G protein (alpha, beta, gamma subunits) pathway. In MAS, the alpha subunit is mutated so as to activate adenylate cyclase, and thus produce high levels of intracellular cAMP. This leads to an increased production of melanin, estradiol, testosterone, thyroxine, growth hormone, and cortisol. Dysregulated production of these hormones results in café-au-lait spots, precocious puberty, fibrous dysplasia, acromegaly,

hyperthyroidism, and Cushing's disease, depending on the tissue harboring the somatic mutation [5].

Skeletal involvement in MAS, especially involving the skull base, is very common. Sarcomatous transformation is reported in less than 1% of cases [6]. Bone scans are useful to detect the extent of the disease, and also for quantifying the skeletal disease burden of FD and predicting the functional outcome.

Hyperthyroidism is a common association in MAS and is reported in 38% of cases [7]. While the development of thyroid cancer in patients with MAS is rare [6], patients should be monitored for this possibility with serial ultrasound or clinical examination.

Primary hyperparathyroidism in MAS is rare and is probably not a part of the syndrome [8]. Secondary hyperparathyroidism, usually due to vitamin D deficiency is common in the general population as well as in FD/MAS [9]. It is established that hyperparathyroidism can worsen FD and should be treated [10]. And total or ionized serum calcium and parathyroid hormone (PTH) should be carefully monitored at regular intervals in all cases of MAS.

Combination of hyperthyroidism and congenital agenesis of thyroid gland in MAS is rare with no documented incidence or genetic association [11, 12]. The co existence of Graves' disease and thyroid hemiagenesis in our patient may be fortuitous.

CONCLUSION

Thus these two cases highlight the various combination of endocrine dysfunction which can co-exist with MAS. Careful histories, examination with proper interpretation of imaging findings are important in guiding the correct management of patients.

REFERENCES

1. McCune DJ. Osteitis fibrosa cystica: the case of a nine-year-old girl who also exhibits precocious puberty, multiple pigmentation of the skin and hyperthyroidism. *Am J Dis Child*. 1936;52:743-747.
2. Albright F, Butler AM, Hampton AO, Smith P. Syndrome characterized by osteitis fibrosa disseminata, areas of pigmentation and endocrine dysfunction, with precocious puberty in females. Report of five cases. *N Engl J Med* 1937; 216:727-746.
3. Weinstein LS, Chen M, Liu J. Gs(alpha) mutations and imprinting defects in human disease. *Ann N Y Acad Sci*. 2002 Jun;968:173-97.
4. Lieberman JA, Koreen AR. Neurochemistry and neuroendocrinology of schizophrenia: a selective review. *Schizophr Bull*. 1993;19(2):371-429.
5. Dumitrescu CE, Collins MT. McCune-Albright syndrome. *Orphanet J Rare Dis*. 2008;3:12.
6. Mastorakos G, Mitsiades NS, Doufas AG, Koutras DA. Hyperthyroidism in McCune-Albright syndrome with a review of thyroid abnormalities sixty years after the first report. *Thyroid*. 1997 Jun;7(3):433-9.
7. 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 Sep;88(9):4413-7.
8. Chapurlat RD, Orcel P. Fibrous dysplasia of bone and McCune-Albright syndrome. *Best Pract Res Clin Rheumatol*. 2008 Mar;22(1):55-69.
9. Shabana W, Delange F, Freson M, Osteaux M, De Schepper J. Prevalence of thyroid hemiagenesis: ultrasound screening in normal children. *Eur J Pediatr*. 2000 Jun;159(6):456-8.
10. Hammami MM, al-Zahrani A, Butt A, Vencer LJ, Hussain SS. Primary hyperparathyroidism-associated polyostotic fibrous dysplasia: absence of McCune-Albright syndrome mutations. *J Endocrinol Invest*. 1997 Oct;20(9):552-8.
11. Barone A, Giusti A, Pioli G, Girasole G, Razzano M, Pizzonia M, Palummeri E, Bianchi G. Secondary hyperparathyroidism due to hypovitaminosis D affects bone mineral density response to alendronate in elderly women with osteoporosis: a randomized controlled trial. *J Am Geriatr Soc*. 2007 May;55(5):752-7.
12. Corsi A, Collins MT, Riminucci M, Howell PG, Boyde A, Robey PG, Bianco P. Osteomalacic and hyperparathyroid changes in fibrous dysplasia of bone: core biopsy studies and clinical correlations. *J Bone Miner Res*. 2003 Jul;18(7):1235-46.