Case Report

Hypothyroidism in McCune–Albright Syndrome and Role of Bone Scan in Management of Fibrous Dysplasia: An Unusual Case Scenario with Review of Literature

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Abstract

The McCune–Albright syndrome (MAS) is a triad of café-au-lait skin pigmentation, precocious puberty (PP), and polyostotic fibrous dysplasia of bone (FD). In general, FD seems to be the most common component of MAS but very rarely precocious puberty can be found in association with café-au-lait skin pigmentation in the absence of FD (about 1% of the cases). Therefore, a more clinically relevant definition of MAS is fibrous dysplasia of bone (FD) and at least one of the typical hyperfunctioning endocrinopathy and/or café-au-lait spots, with almost any combination possible. Bone scan can be the modality of choice to look for bone disease burden of fibrous dysplasia in most patients of MAS and may change the management accordingly. Most of the cases of MAS reported worldwide are associated with hyperthyroidism, up to best of our knowledge on the basis of literature search in pubmed and Google; no case was reported with hypothyroidism. Herein, we report a 12-year-old girl diagnosed with MAS and associated hypothyroidism.We have also reviewed the MAS related literature.

Key words: *Fibrous dysplasia, hypothyroidism, McCune–Albright syndrome, pituitary macroadenoma, precocious puberty*

Introduction

The McCune–Albright syndrome (MAS) was first described in 1936 by McCune and separately by Albright as a triad of café-au-lait skin pigmentation, precocious puberty (PP), and polyostotic fibrous dysplasia (FD) of bone.[1,2] Later on it was recognized that multiple endocrinopathies could be associated with primary triad.

The most common form of autonomous endocrine hyperfunction in this syndrome is gonadotropin independent precocious puberty but affected individuals may also have autonomous hyperfunction of other endocrine glands such as hyperthyroidism,[3] renal phosphate wasting with or without rickets/osteomalacia, growth hormone (GH) excess, and Cushing syndrome could be found in association with the original triad.[4] Rarely, nonendocrine systems in MAS may also be involved, such as liver, cardiac, parathyroid, and pancreas.[5] Now it is well understood that MAS is rare condition but FD is not. FD can be monostotic FD, or polyostotic FD.[6]

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Most of the cases of MAS reported worldwide are associated with hyperthyroidism, up to best of our knowledge on the basis of literature search in pubmed and Google; no case was reported with hypothyroidism. Herein, we report a 12-year-old girl diagnosed with MAS and associated hypothyroidism.

Case Report

A 12-year-old girl who born out of non consanguineous marriage was apparently asymptomatic till 5 years of age, when her mother noticed breast development followed by intermittent vaginal spotting till age of 10 years. But they never consulted any doctor for these symptoms. In 2009, she sustained pathological fracture in left femur after fall from standing

How to cite this article: Kumar N, Kheruka SC, Singh RR, Ravina M, Dutta D, Gambhir S. Hypothyroidism in mccune-albright syndrome and role of bone scan in management of fibrous dysplasia: An unusual case scenario with review of literature. Indian J Nucl Med 2017;32:25-9.

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Access this article online

Website: www.ijnm.in

DOI: 10.4103/0972-3919.198462

Quick Response Code:

height; there was no further history of recurrent fracture or bone pain. From last 3 months she developed headache and visual field defects. She had history of prominence of right maxilla and right skull bone also. Patient was evaluated at other hospital for headache and visual field defects. MRI brain showed pituitary macroadenoma [Figure 2 and Figure 3] and she was referred to our hospital for further management. Bone scan [Figure 4] and X-ray skeletal survey [Figure 5 and Figure 6] was done suggestive of polyosteotic fibrous dysplasia. On hormone evaluation, she was found to have acromegaly (unsuppressed growth hormone and raised IGF-1) secondary hypothyroidism, secondary hypocortisolism with mild hyperprolactinemia [Table 1].

Hormone profile

In physical examination the weight was 44 kg (75th percentile), height was 146.5 cm (25–50th percentile), breast stage 5, pubic hair stage 4 (according to Tanner Score), vitals stable (BP 100/60 mmHg, pulse rate 76/min), She was conscious, oriented with coarse facies, prominence of right maxilla and parietal bone, multiple

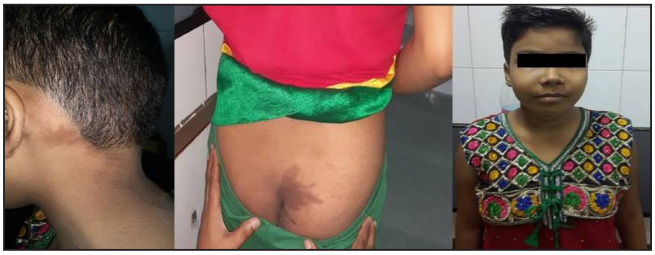

Figure 1: Image reveals prominence of right maxilla and parietal bone, multiple cafe-au-lait spots on back.

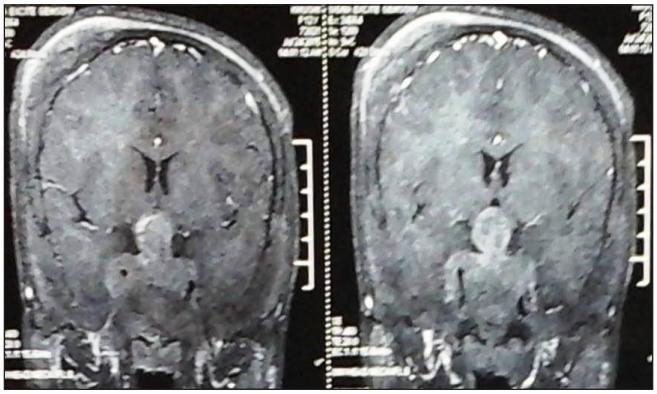

Figure 2: MRI brain coronal T1 weighted postcontrast images reveal heterogeneously contrast enhancing hyperintense sellar and suprasellar mass lesion extending laterally into cavernous sinuses and encasing both internal carotid arteries. Diffuse calvarial thickening and expansion in right high parietal region is also present.

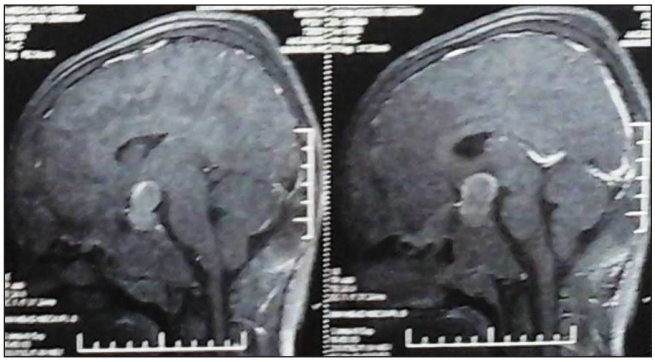

Figure 3: MRI brain sagittal T1 weighted post contrast images reveal heterogeneously contrast enhancing hyperintense sellar and suprasellar mass lesion extending superiorly up to the floor of the third ventricle and pushing the optic chiasma superiorly and anteriorly

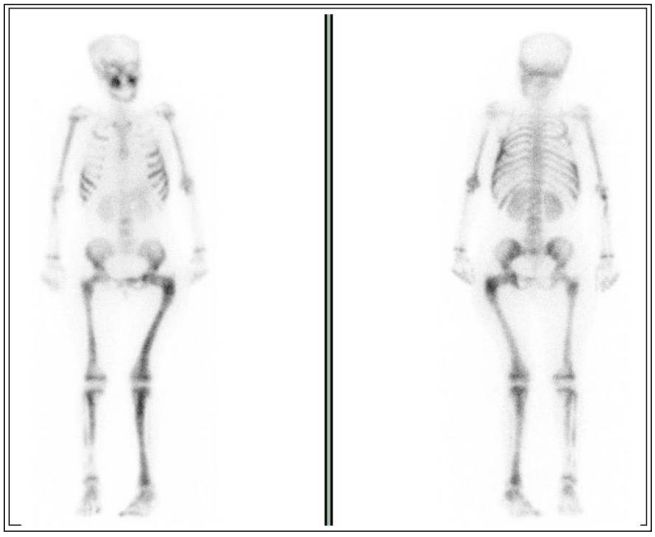

Figure 4: The whole body 99m-Tc-MDP bone scan image reveals multiple regions of intense activity on the right side of the skull, mandible, right humerus, scapula, hemi pelvis, femur and tibia. Foci of increased uptake were also present in the lumbar spine and the left humerus.

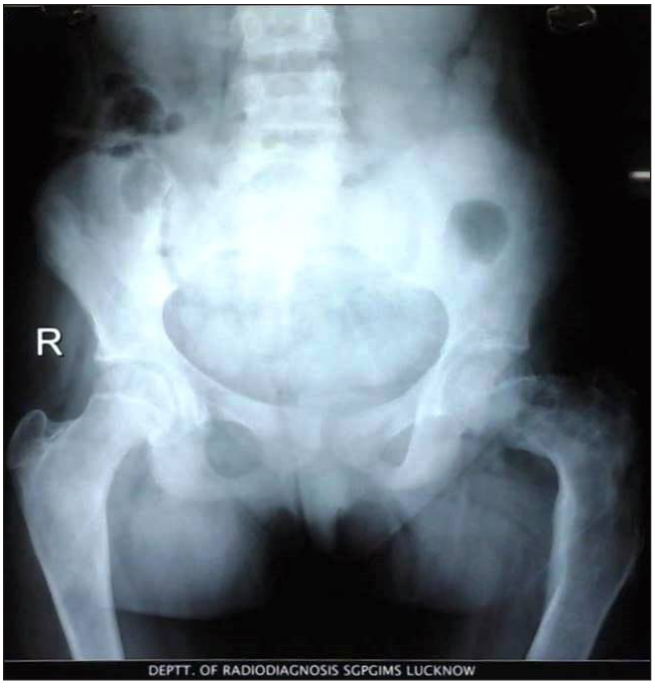

Figure 5: X-ray pelvis AP view showing expensile radiolucent lesion with sclerotic foci in neck and metaphysis of B/L femur with sephered cook deformity on left side.

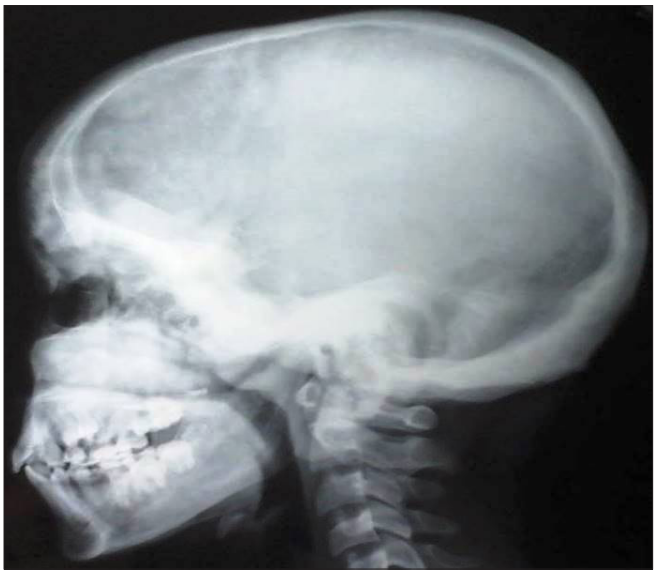

Figure 6: A plain X-ray film lateral view shows extensive involvement of skull base with thickening and sclerotic changes.

Table 1: Hormone profile of patient

Investigation	Value	Postreatment value	Normal range
Serum cortisol			
Simple 8 am	[82] nmol/L		110–520 nmol/L
Stimulated (60 min)	[403] nmol/l		
fT4	9.42 pmol/L	13.8 pmol/L	11.5–22. pmol/L
T4 (Thyroxine)	65.8 nmol/L	72 nmol/L	57-148 nmol/L
Serum prolactin	1419 IU/mL		
Serum growth hormone (120 min)	31.41 ng/mL		0–20 ng/mL
Growth hormone suppression	>35.0 ng/mL		<1 ng/ml
0 min	33.13 ng/mL		
60 min postglucose	[31] ng/mL		
120 min postglucose			
IGF-1	485 ng/mL		

cafe-au-lait spots on back and thighs [Figure 1]. She was found to have bitemporal hemianopia. Her systemic examination was normal.

Investigations: Her blood investigations were suggestive of unsuppressed growth hormone, raised IGF-1, mild hyperprolactinemia, secondary hypocortisolism, secondary hypothyroidism, and microcytic hypochromic Anemia. MRI brain coronal and sagittal T1 weighted post contrast images reveal heterogeneously contrast enhancing hyperintense sellar and suprasellar mass lesion extending laterally into cavernous sinuses and encasing both internal carotid arteries, superiorly reaching up to the floor of the third ventricle and pushing the optic chiasma superiorly and anteriorly. Plain X-ray film lateral view shows extensive involvement of skull base with thickening and sclerotic changes. X-ray pelvis AP view showing expansile radioluscent lesion with sclerotic foci in neck and metaphysis of B/L femur with sephered cook deformity on left side.

Radionuclide bone scan was done after I.V injection of 20 mCi of 99m-Tc MDP. Whole body anterior and posterior images were acquired in projections after 3 h. SPECT-CT of the thoracic region was done subsequently with low dose 2.5 mA X-rays and images were displayed in transaxial coronal and sagittal projections. Images reveal increased tracer uptake in bilateral maxillae, multiple bilateral ribs, bilateral humerus, bilateral SI joint, bilateral femur (left > right), bilateral tibia and fibula (left > right). SPECT-CT images reveals increased tracer uptake with lytic lesions in the background of sclerosis at the aforementioned sites. In view of clinical history and image findings, her diagnosis was confirmed as polyostotic fibrous dysplasia.

Final diagnosis and management: Final diagnosis was McCune–Albright syndrome with classical component, that is, caif-au-lait spots and precocious puberty, polyostotic fibrous dysplasia, pituitary macroadenoma with mass effect which leads to secondary hypothyroidism and secondary hypocortisolism. Patient was managed with thyroxine, prednisolone, calcium, and vitamin D3 supplement along with zoledronic acid. Treatment with 50 µg of thyroxin and 2.0 mg of prednisolone twice a day improves the thyroid profile but there was no significant change in cortisol hormone level.

Discussion

McCune–Albright syndrome is a rare condition which affects multiple systems, Donovan McCune and Fuller Albright first described it separately in 1937, in a group of children with skin pigmentation, bone deformities, and endocrinal disorders which develops due to an activating mutation in the Gs gene.[7,8] The disorder occurs due to postzygotic somatic mutation in the gene GNAS 1 on chromosome 20q13-13.29,[9] this gene is responsible for coding for the alpha subunit of stimulatory G protein. The number of mutated cells and the affected organs decides the clinical expression.

MAS is diagnosed on the triad of FD, endocrinopathy, and hyperpigmentation of the skin. The classical form of MAS is more common in females. Bone dysplasia is revealed in the first decade by aching pain, pathological fractures, limb asymmetry, and deformities. Abnormal fibrous tissue growth occurs in many bones, especially in the long bones, ribs, and skull bones. Café-au-lait macules (CALMs) usually develop between the age of 4 months and 2 years, but it may be present at birth.

In McCune–Albright syndrome, polyostotic fibrous dysplasia may exhibits a wide spectrum of clinical severity.

Patients with extensive bone disease may present in early childhood with fractures and deformities of the long bones like femur which leads to shepherd's crook deformity.[10] Due to limb length discrepancies patients with moderate bone disease may present with difficulty in ambulation. Patients with mild bone disease without fractures or deformities are usually detected with a radiographic examination. Classical radiographic findings reveal replacement of normal trabecular architecture by a widened medullary cavity and cortical thinning with a ground glass appearance.

In mildly affected patients in whom even radiography may fail to identify active fibrous dysplasia, especially when regions such as the base of the skull are affected, bone scan is superior to conventional radiology to establish the extent of bony involvement.[11,12]

In our case, conventional radiography revealed facial asymmetry, skull base thickening, fracture left femur, and well known shepherd's crook deformity; however, bone scan reveals a wide spectrum of skeletal involvement, that is, bilateral maxillae, multiple bilateral ribs, bilateral humerus, bilateral SI joint, bilateral femur (left > right), bilateral tibia, and fibula (left > right) which were not identified on X-rays. Hence, we also concluded that bone scan has a definitive role to establish extent of disease burden and may change the management accordingly and it should be the modality of choice to look for bone disease burden of fibrous dysplasia in most patients of MAS.

Hyperthyroidism is a common autonomous endocrinopathy in the patient of MAS (38%).[13] Patients are clinically euthyroid but biochemically there is suppressed thyroid stimulating hormone with raised triiodothyronine. Later, some may develop frank hyperthyroidism; therefore, there should be regular follow-up with T3, free thyroxine (FT4), thyroxine (T4), and TSH. Ultrasound can be performed to look for anatomical abnormality of thyroid gland.

An interesting finding in our case was the unique presentation of various endocrinopathies, as overproduction of growth hormone and prolactinemia (likely due to activating mutation in the Gs gene), whereas on other hand there was hypothyroidism and hypocortisolism (most likely attributed to the pressure effect of pituitary macroadenoma on the normal functioning pituitary tissue).

To best of our knowledge, in literature majority of the reported cases of MAS are associated with hyperthyroidism and this is the first case of MAS associated with hypothyroidism.

Till now definite treatment for MAS is not available, also there is no technique to diagnose MAS in prenatal period. But now by novel polymerase-chain-reaction-based techniques, activating mutation in the peripheral blood of patients with MAS has been successfully detected, which might help in diagnostic as well therapeutic areas.[14]

For effective treatment of MAS, all endocrine-related disorders which adversely affect the bone health should be screened.[15] This includes PP, hyperthyroidism, Cushing's syndrome, GH excess, and secondary hyperparathyroidism. Bisphosphonates are frequently used in the treatment of FD.[16] Earlier thinking to use the bisphosphonates in FD was that they would stop the progression of disease. But now this has been concluded that bisphosphonates have no effect on the natural history of the fibrous dysplasia.[17] Maintaining the musculature around the FD bone is important for protecting the bone. Therefore, strengthening exercises and strength maintenance is important to minimize the risk for fracture.

Conclusion

MAS has been reported in multiple studies worldwide, but most of the reported cases in the literature are associated with hyperthyroidism. We report a patient of MAS associated with hypothyroidism which is a unique finding. Secondary hypothyroidism or other pituitary hormonal deficiencies are likely to be due to pressure effect of pituitary adenoma on normal pituitary tissue. The goal of treatment of pituitary macroadenoma is complete cure. When this is not possible, reducing tumor mass, restoring hormone function, and restoring normal vision are attempted using medications, surgery, and radiation. Secondary hypothyroidism could be easily managed with thyroxin replacement therapy. Bone scan has a definitive role to establish extent of disease burden and may change the management accordingly.

Financial support and sponsorship

Nil

Conflicts of interest

There are no conflict of interest.

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