

CASE REPORT

MCCUNE ALBRIGHT SYNDROME PRESENTING AS PRECOCIOUS PUBERTY

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ABSTRACT: We describe a case of 5 years old female child, who presented to us with complaints of precocious puberty and skin pigmentation. Her x-rays done for ascertaining the age showed findings suggestive of fibrous dysplasia. Keeping in mind her presentation and x-rays, a diagnosis of McCune Albright syndrome was suspected and was later confirmed with some more laboratory and imaging findings.

KEYWORDS: McCune Albright Syndrome precocious puberty, fibrous dysplasia.

INTRODUCTION: McCune-Albright syndrome (MAS) is a rare genetic disease that is defined as an association of polyostotic fibrous dysplasia, café au lait spots and precocious puberty. Other endocrine syndromes associated with MAS are hyperthyroidism, acromegaly, gonadotropinomas, hyperprolactinemia, cushing syndrome, hyperparathyroidism, gynaecomastia and hypophosphatemic rickets among few.

CASE REPORT: A five years old girl child presented to us with the complaint of premature development of breasts. She had history of irregular menstrual bleeding for the last 2 years. There was also history of bone pains in lower limbs after running or long walks since 2-3 years. There was no history of any drug intake in the past. On general physical examination, she had multiple dark, pigmented patches on the back (Fig. 1). She was taken up for routine investigations, which were normal.

Serum phosphorus levels were low. Serum alkaline phosphatase levels were significantly high. Serum dihydroxy cholecalciferol levels were high. Thyroid profile and serum calcium was within normal limits.

On radiography, X-Ray of both knees showed evidence of areas of increased density and radiolucency in the lower part of femur, more so on right side.

X-Ray of skull, lateral view was taken, which showed thickening of skull vault with sclerosis at the base and paranasal sinuses. Radiolucent areas were also seen in skull vault. X-Ray of pelvis showed heterogeneous areas in the iliac bone and upper end of femur on both sides. All of these X-Ray findings were corroborative with polyostotic type of fibrous dysplasia. X-Ray of both hands was also done to ascertain age, which came out to be bone age of 11-16 years.

Her MRI brain was done which revealed generalized diffuse thickening of craniofacial bones with encroachment of the paranasal sinuses, mastoid air cells as well as the orbital apices (Fig. 2, 3, 4, 5). A possibility of McCune Albright syndrome was kept in mind as the patient had presented with precocious puberty.

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DISCUSSION: McCune-Albright syndrome (MAS) is a rare genetic disease that is defined by the triad of polyostotic fibrous dysplasia of bone (FD), café-au-lait skin pigmentation and precocious puberty (PP).^[1] It was first described by Donovan James McCune and Fuller Albright in 1937. MAS is a rare disease and its estimated prevalence ranges between 1/100, 000 and 1/1000, 000.

It has been shown recently that mutations in the regulatory G_s alpha protein (encoded by GNAS gene) are the underlying etiology.^[2] The extent of the disease is determined by the proliferation, migration and survival of the cell in which mutation spontaneously occurs during embryonic development.

Other endocrine syndromes associated with MAS are hyperthyroidism, acromegaly, gonadotropinomas, hyperprolactinemia, cushing syndrome, hyperparathyroidism, gynaecomastia and hypophosphatemic rickets among few. Rarely, other organ systems may be involved (liver, cardiac, parathyroid, pancreas).^[3]

The clinical presentation of MAS is highly variable, depending on which of the various potential components of the syndrome predominate. Patient generally presents with sign and symptoms of precocious puberty or fibrous dysplasia of bones. Presence of café au lait spots is most commonly found in patients of MAS, but is rarely a presenting sign. Females presenting with precocious puberty, usually have history of cyclical or irregular vaginal bleeding or spotting, early development of breasts, usually without development of pubic hair and sexual precocity. In case of males, presentation is generally with penile and testicular enlargement, pubic and axillary hair, scrotal rugae and precocious sexual behaviour.

Patients with fibrous dysplasia usually presents with limping or gait anomalies, visible bony deformities, bone pains but occasionally a pathological fracture may be the presenting complaint. Symptoms begin usually in childhood, although in some cases, disease is clinically silent and discovered incidentally on X-Rays. Spontaneous resolution of bone lesions does not occur. These lesions may worsen or new lesions may appear with time. Bone lesions have been seen to worsen in pregnancy; this may be due to effect of estrogen excess. Malignant transformation of fibrous dysplasia lesions is the most common malignancy that occurs in association with MAS.^[4]

Benign intramuscular myxomas are a common entity in the patients having fibrous dysplasia of bones also known as Mazabraud's syndrome, commonly present in adult life as complaint of palpable masses in limbs, abdominal wall or back. These often are asymptomatic but may be painful.

Café au lait spots seen in MAS are fairly predominant, with irregular edges and are called "coast-of-Maine" variants (Different from the smaller, rounder, smooth edged "Coast-of-California" café au lait spots associated with neurofibromatosis type 1). These spots are large and less numerous than those in NF-1.

A few cases have been described in which MAS has been associated with either patchy or diffuse alopecia.

Thyroid anomalies are also found in 30-40% of patients with MAS. A few patients having growth hormone excess present with acromegaly.

Diagnosis of MAS is mainly on the basis of clinical grounds. In patients with sexual precocity, LH, FSH may be below normal limits. In females, estrogen levels are affected. In

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males, serum free and total testosterone levels may be elevated. Blood and urine biochemistry may show evidence of excessive bone turn over and elevated indicators for bone formation and resorption. Serum alkaline phosphatase and osteocalcin levels are elevated.

Plain radiographs are often sufficient to make the diagnosis of fibrous dysplasia. On plain bone radiographs, multiple areas of bony lysis and sclerosis are seen. The lesions usually arise in the medullary cavity and expand outward replacing normal bone, which results in thinning of the cortex. It is usually the metaphysis and / or the diaphysis that are involved, epiphysis are spared. Skull base and the proximal femur are the sites most commonly involved along with tibia and ribs. Fibrous dysplasia in the craniofacial bones tends to have sclerotic appearance on X-Rays. CT scanning is the best modality for imaging lesions in skull, which reveals "ground glass" appearance. MRI of the brain is also useful, particularly when bone cysts are present. Development of cystic lesions is also common in older patients in longer bones as well as in craniofacial bones.

Formal bone age estimation may be higher in patients with sexual precocity.

Isotope bone scanning is the most sensitive tool for detecting fibrous dysplasia lesions. They are useful for not only detecting the extent of the disease, but for qualifying the skeletal disease burden and predicting functional outcome.^[5] Ultrasonography may be a useful tool to examine patients with soft tissue swellings of myxoma.

Biopsy of the fibrous dysplasia lesions is confirmatory if in doubt on radiography. On characteristic finding is the absence of lamellation pattern seen in normal bone. The bony lesions are rich in spindle- shaped fibroblasts, with a swirled appearance within the marrow space and erratically arranged 'tongues' of woven bone, also known as Chinese writing pattern.

Genetic testing is possible but is not routinely used as it is not easily available. In most of the cases, genetic testing contributes little to the diagnosis.

Differential diagnosis include neurofibromatosis, osteofibrous dysplasia, non-ossifying fibroma, ovarian neoplasm and idiopathic central precocious puberty. For medical management, bisphosphonates can be used for fibrous dysplasia. For precious puberty, aromatase inhibitors like letrozole and tamoxifen, estrogen agonist / antagonist has been in use. For growth hormone excess, long acting somatostatin analogues and GH antagonists like pegvisomant has been proved to be useful. Surgery has been used in cases of fibrous dysplasia and GH excess among others. Radiotherapy is an option when surgical treatment is not possible and medicinal treatment fails.

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Fig. 1: Multiple dark pigmented patches present on the skin of back



Fig. 2: T1W sagittal image depicting the thickened skull base. The paranasal sinuses are obliterated. The pituitary gland (arrow) is normal

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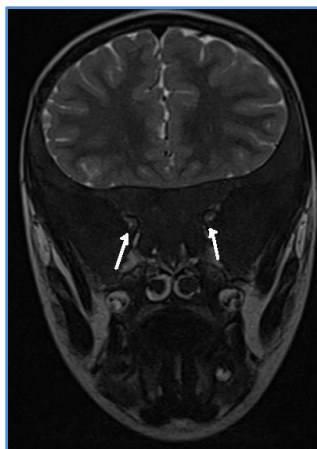


Fig. 3: T2W coronal image depicting the thickened skull base at the level of the orbital apices (arrows)

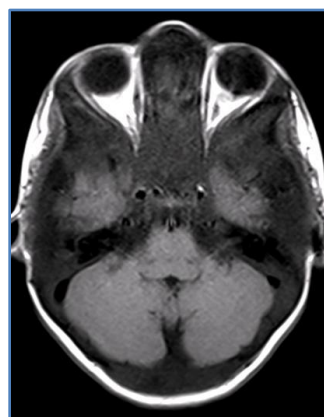
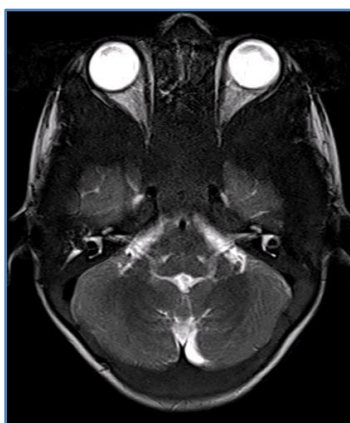


Fig. 4: A and 4B T2W and T1W images in axial plane showing marked thickening of skull base. Note encroachment of the mastoid air cells

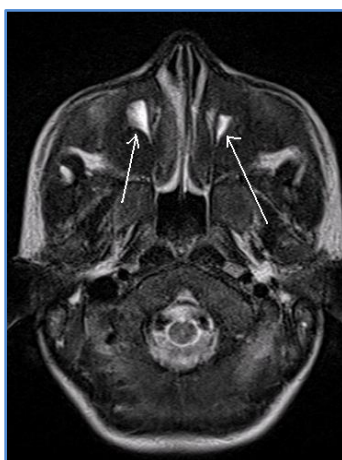


Fig. 5: T2W axial image showing obliterated maxillary sinuses (arrows)

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