McCune-Albright syndrome (MAS): a perspective

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**ABSTRACT**

The McCune-Albright syndrome (MAS) is a rare, sporadic disease characterized by a classical triad of clinical signs: polyostotic fibrous dysplasia, skin hyperpigmentation and endocrine dysfunction. The disease is caused by postzygotic, somatic mutations at codon 201 of the GNAS gene that results in cellular mosaicism, thus leading to a broad spectrum of clinical manifestations. The major endocrine disorders include autonomous hyperfunction of several endocrine glands, such as gonads, thyroid, pituitary and adrenal cortex, i.e. glands sensitive to trophic agents acting through cAMP dependent pathway. Since specific treatment is required, the prognosis depends on the severity of each individual endocrine and non-endocrine manifestation. As mutation detection rates may vary considerably according to the type of tissue analyzed and the detection method used, sensitive and specific molecular methods must be used to look for the mutation from all available affected tissues and from easily accessible tissues, particularly in the presence of atypical and monosymptomatic forms of MAS. This review will briefly summarize the clinical manifestations and the most recent data on genetics and molecular diagnostic of the disease.

1. **INTRODUCTION**

McCune-Albright Syndrome (MAS) is a rare multisystem disorder characterized by (1) replacement of normal bone tissue with areas of abnormal fibrous growth; (2) patches of abnormal skin pigmentation (i.e., areas of light-brown skin [cafe-au-lait spots] with jagged borders); abnormalities in the glands that regulate the body's rate of growth, its sexual development, and certain other metabolic functions (multiple endocrine dysfunction). Depending on the number and location of the skeletal abnormalities, mobility may be impaired, as well as vision and/or hearing, and the individual may experience substantial pain. McCune-Albright Syndrome is the result of a genetic change (mutation) that occurs randomly, for no apparent reason (sporadic). In individuals with the disorder, this sporadic genetic mutation is present in only some of the body's cells (mosaic pattern). The symptoms and physical characteristics associated with the disorder vary greatly from case to case, depending upon the specific body cells and tissues that are affected by the genetic mutation. This mutation occurs after fertilization (postzygotic somatic mutation). The range of severity of the disorder is very broad: some children are diagnosed in early infancy with obvious anomalies of bone and increased hormone production by one or more of the endocrine glands; others show no evidence of bone, skin or endocrine malfunction in childhood and may enter puberty at an appropriate age. McCune-Albright syndrome (MAS) is caused by postzygotic, activating mutations of the α-subunit of the stimulatory G protein (G\(_{\alpha}\)) that is coupled to many cell surface hormone receptors. The clinical manifestations of the disorder are variable due to the somatic nature of the mutations and the mosaic distribution of affected tissues. These are now recognized to extend well beyond the classic triad of precocious puberty, fibrous dysplasia of bone, and café-au-lait skin pigmentation, and include nonendocrine manifestations such as renal phosphate wasting, hepato-biliary dysfunction, and heart disease. Hyperfunctioning endocrinopathies include gonadotropin-independent precocious puberty, hyperthyroidism, GH excess, hyperprolactinemia, and hypercortisolism. Hypercortisolism, or Cushings syndrome, affects a minority of patients with MAS and has a quite heterogeneous natural history, ranging from spontaneous resolution to need for adrenalectomy or even death. Due to the small number of reported patients, it may be difficult for the clinical practitioner to recognize which patients can be safely monitored or treated medically vs. those patients at high risk of morbidity and mortality who may benefit from prompt adrenalectomy. In addition, long-term outcomes of these patients have not been reported. To address questions regarding diagnosis, prognosis, management, and long-term outcome of this disorder, we analyzed our eight cases of MAS and cortisol excess and reviewed the 21 cases from the literature and one additional case from personal communication.

2. **ETIOLOGY**

The observation that the G protein/cAMP/adenylate cyclase signaling pathway was central to all of the tissues involved in MAS eventually led to the discovery that mutations in the regulatory G\(_{\alpha}\) protein (encoded by the GNAS gene) were the underlying molecular etiology of MAS. In all published cases of MAS, PFD, and even MFD, activating mutations of G\(_{\alpha}\) at the R201 position have been identified. More recently, mutations at the Q227 position have been found in association with FD. The lack of vertical transmission of the disease, along with the observation that skin and bone lesions tend to respect the midline and be on one or the other side of the body, has led to the unproven, but accepted, concept that the disease is the result of...
postzygotic mutations, and that patients are therefore somatic mosaics. The point in time in development at which the mutation occurs, the specific cell in which it occurs, and to where its progeny migrate, determines what tissues will be affected, and thus the phenotype. Therefore, in cases in which tissues of endodermal, mesodermal, and ectodermal origin are involved, it would appear that the mutation occurred at the inner cell mass stage.

3. SYMPTOMS AND PRESENTATION

Mutation of the GS gene in chromosome 20q13 occurs early in development, and results in a mosaic of abnormal and mutated cells. The manifestations of MAS in each individual depend upon the extent and distribution of abnormal cells. Abnormal and prolonged activation of multiple peripheral endocrine glands occurs even while the necessary stimulatory pituitary hormones may be absent. Precocious puberty, with onset of breast development, pubic hair, and the onset of menses as early as the first few months of life may occur in females. Other manifestations include acromegaly, hyperthyroidism, hyperprolactinemia, and others. Frequently involved bones include the femur, the tibia, the facial skeleton, and the ribs. Bone fragility and associated fractures are common, and weight-bearing bones may suffer multiple fractures. In the proximal femurs, multiple successive cortical microfractures may result in characteristic bowing of the proximal end of the bone into a “shepherd's crook” deformity.

4. X-RAY APPEARANCE AND ADVANCED IMAGING FINDINGS

On radiographs, the affected bones have multiple, expansile, mostly lucent lesions which contained a fine matrix described as “ground glass.” The normal trabecular pattern is absent. The tumors are a radiolucent area with a sclerotic rim, and may slightly expand or thin the nearby bone cortex. The matrix of the lesion has a “milky” or “ground glass” appearance due to the very fine bony trabeculae contained within the tumor. On bone scan, fibrous dysplasia lesions typically demonstrate increased uptake. However, 10% to 15% of lesions do not have increased radiotracer uptake and appear “cold” on bone scans.

5. HISTOPATHOLOGY FINDINGS

The pathological findings in the involved bones include classic features of fibrous dysplasia. On microscopic analysis, there is fibrous connective tissue containing immature trabeculae of a woven, non-lamellar bone. These immature trabeculae may have a characteristic “Chinese letter” or “alphabet soup” appearance, resembling partially formed letters or symbols.

6. TREATMENT OPTIONS FOR THIS TUMOR

Treatment depends on the manifestations and extent of the disease. Bone fracture lead to the need for orthopedic stabilization and joint replacement due to periarticular fractures. Pamidronate treatment of patient’s with polyostotic fibrous dysplasia has shown encouraging results. Pamidronate seems to reduce the fracture rate and reduce the bone pain associated with the lesion. The benefit of pamidronate in polyostotic fibrous dysplasia has been conclusively demonstrated. Bone pain, fracture risks, bone density, and metabolic indices of bone turnover show favorable response to treatment. However, some authors have reported that in developing children, dysplastic lesions in long bones continued to undergo expansion despite pamidronate treatment. For developing children, the authors of this website recommend early and aggressive intervention with pamidronate, and orthopedic stabilization of at-risk long bones, using appropriate expandable or non-expandable intramedullary devices. The femoral neck and proximal femur are at particularly high risk, and early prophylactic intramedullary noding with a cephalomedullary device is recommended, before the microfractures and deformity begin to develop.

7. CONCLUSION

Comorbid heart and liver disease were poor prognostic markers and may indicate the need for prompt adrenalectomy. The high incidence of cognitive disorders indicates a need for close developmental follow-up and parental counseling. Patients with spontaneous resolution of CS may develop adrenal insufficiency, and they require long-term monitoring.

REFERENCE