McCune–Albright Syndrome
Pathophysiology, Diagnosis, and Management

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Summary
McCune-Albright syndrome (MAS) is an extremely heterogenous condition in which a variety of systemic and endocrine abnormalities can occur. It is classically characterized by the triad of peripheral precocious puberty, café au lait skin pigmentation, and polyostotic fibrous dysplasia of bone. It is caused by activating mutations of GNAS, the gene encoding the alpha subunit of the stimulatory G-protein ($G_\alpha_S$), and result in constitutive, ligand-independent activity in affected cells. The $GNAS$ activating mutations lead to a loss of intrinsic guanosine triphosphatase (GTPase) activity of $G_\alpha_S$, resulting in an inability to return the cell to its inactive basal state after stimulation by a hormone ligand. Thus, the presence of $GNAS$ mutations in endocrine cells is associated with unregulated hormone production and the development of endocrine cells is associated with unregulated hormone production and the development of endocrine hyperfunction. Diagnosis is based on careful physical examination as well as biochemical and radiographic evaluation, while molecular diagnosis is currently best reserved for the research setting. Therapeutic approaches vary widely and must be individualized to target the presiding manifestations of the disorder. Because MAS is both rare and heterogeneous in nature, collaborative and multi-center research efforts are paramount to advance the understanding of the etiology, pathophysiology, diagnosis and treatment of this condition.

Key Words: G-protein-coupled receptor; $G_\alpha_S$; $GNAS$; Precocious puberty; Café au lait skin pigmentation; Fibrous dysplasia of bone.
INTRODUCTION

Case Vignette

A 2-year-old boy presented to the pediatric endocrinology clinic with failure to thrive. Thyroid function tests performed as part of the medical evaluation revealed a suppressed serum thyrotropin-stimulating hormone level, and the rest of the laboratory evaluation was unremarkable. Subclinical hyperthyroidism persisted without biochemical evidence of Graves’ disease. Although he did not present with other manifestations of the disorder, McCune–Albright syndrome (MAS) was included in the differential diagnosis of his hyperthyroidism. A bone scan to screen for fibrous dysplasia of bone was obtained and revealed multiple areas of increased uptake. Subsequently, he was noted to have café au lait skin pigmentation between the buttocks (Fig. 1), and a diagnosis of MAS was made.

MAS is classically defined as the clinical triad of precocious puberty (PP), café au lait skin pigmentation, and polyostotic fibrous dysplasia of bone. Scientific advances in the understanding of the molecular basis of the syndrome have provided grounds for clinical insight with regard to the pathophysiology of MAS and the phenotypic heterogeneity among patients. Atypical presentations are increasingly recognized, as was the case in the child described above. As a result, the evaluation and treatment of patients with MAS has evolved and is guided by the knowledge of the specific manifestations of the disease that continue to emerge.

HISTORY

The first published case reports of girls with the constellation of PP, café au lait skin pigmentation, and polyostotic fibrous dysplasia of bone are in the German medical literature from the early 1900s (1,2). Drs Donovan James McCune and Fuller Albright first described this clinical presentation as a syndrome at the Society for Pediatric Research Annual Meeting in 1936 (3). Here, they reported the case of a 9-year-old girl with a medical history of severe neonatal jaundice, dark brown skin patches, osteitis fibrosa cystica with bony deformities, onset of menarche at the age of 2 years, and hyperthyroidism. Shortly after the original description, case reports of patients with phenotypic evidence of the syndrome were published by McCune (4,5) and Albright (6), who astutely speculated that the disease was due to a defect in embryological development.

Fig. 1. Café au lait skin pigmentation noticeable between the buttocks.