

# HOSPITAL PHYSICIAN®

## PEDIATRIC ENDOCRINOLOGY BOARD REVIEW MANUAL

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The *Hospital Physician Pediatric Endocrinology Board Review Manual* is a study guide for fellows and practicing physicians preparing for board examinations in pediatric endocrinology. Each manual reviews a topic essential to the current practice of pediatric endocrinology.

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## Gonadotropin-Independent Precocious Puberty

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## Table of Contents

Introduction .....	2
Major Causes: Incidence, Underlying Defect, and Key Features.....	2
McCune-Albright Syndrome .....	6
Familial Male Precocious Puberty .....	8
Congenital Adrenal Hyperplasia.....	9
Conclusion .....	10
References .....	10

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# Gonadotropin-Independent Precocious Puberty

Jill D. Jacobson, MD

## INTRODUCTION

This manual is the second in a two-part review of precocious puberty. The first half of the review began with an overview of normal puberty and a discussion of the general clinical approach to the child who presents with one or more signs of early puberty. This was followed by clinical cases highlighting the approach to evaluation and management of patients with partial and gonadotropin-dependent forms of precocious puberty.

In this half of the review, the discussion turns to the less common forms of precocious puberty (ie, gonadotropin-independent forms). Whereas *gonadotropin-dependent precocious puberty* (GDPP) involves hypothalamic release of gonadotropin-releasing hormone (GnRH) in a pulsatile manner, as normally occurs in puberty, *gonadotropin-independent precocious puberty* (GIPP), also referred to as *peripheral precocious puberty*, involves early gonadal steroid production that is independent of gonadotropin stimulation. Some of the causes of GIPP are listed in **Table 1**. The main sources of steroid hormone excess in GIPP include the ovary, the testis, and the adrenal gland. The approach to and management of the main causes of GIPP are discussed individually according to the specific underlying diagnosis. Although there is some controversy about the normal age of onset of puberty in boys and girls,<sup>1-3</sup> this review uses the original Marshall and Tanner definition (ie, age 8 years in girls and age 9 years in boys).<sup>4,5</sup>

## MAJOR CAUSES: INCIDENCE, UNDERLYING DEFECT, AND KEY FEATURES

### McCUNE-ALBRIGHT SYNDROME

McCune-Albright syndrome (MAS) was originally described in 1937 as a triad of precocious puberty, café-au-lait spots, and lytic bone lesions occurring in girls.<sup>6</sup> The cause was identified in 1991 as a constitu-

tively activating mutation in the gene that encodes the  $\alpha$  subunit of the stimulatory G protein ( $G_s\alpha$ ) (**Figure 1**).<sup>7</sup> The gene is named *GNAS1* for the guanine nucleotide  $\alpha$  subunit.  $G_s\alpha$  is involved in the action of a multitude of hormones and other mediators. Indeed, since the original description of MAS, the clinical phenotype has been expanded to include several other endocrine conditions including hyperthyroidism, acromegaly, and Cushing syndrome.<sup>8</sup> **Table 2** lists the known endocrine abnormalities seen in MAS along with the implicated hormonal mediator. Several nonendocrine problems have also been described in MAS. Histamines are noted to exert actions via  $G_s\alpha$ , and patients with MAS have been reported to display an increased responsiveness to histamines and a higher risk for allergies.<sup>9</sup> Males are at an increased risk for testicular microlithiasis.<sup>10</sup>

The cutaneous hyperpigmentation in MAS follows the lines of Blaschko (ie, along dermatomes) (**Figure 2**). This pigmentation pattern reflects the dorsoventral outgrowth of two different populations of cells during early embryogenesis; the pattern is seen in chimeric individuals. As all cases of MAS are sporadic, it is postulated that the  $G_s\alpha$  mutation is lethal and that only chimeric individuals survive.<sup>11</sup> Patients with MAS display varying degrees of chimerism and therefore varying degrees of clinical severity. The presentation of MAS can range in severity from early neonatal death resulting from cardiac hypertrophy (presumably related to catecholamine and/or  $\beta$ -adrenergic receptor activation) to single lytic bone lesions in the absence of other endocrine problems.<sup>8</sup>

MAS predominantly affects females. Although the cause of the sexual dimorphism is unknown, one hypothesis is that there is an ascertainment bias; that is, more females are referred for precocious puberty and premature menarche, whereas males display more subtle signs of puberty. Data from the Italian Multicenter Study Group on MAS revealed that the age at diagnosis of MAS was significantly lower in girls than in boys. In that study, girls also displayed a significantly higher prevalence as well as an earlier onset of GIPP compared with boys.<sup>12</sup>

MAS is classified as a rare disease, affecting fewer