

Clinical Manifestations of Precocious Puberty and Associated Heritable Diseases: A Case Report

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Abstract

The incidence of sexual precocity is 1:10,000, yet previous puberty is infrequently reported. We report a unique case of a young child presenting to the Dermatology clinic for management of acne vulgaris and precocious puberty prompting further work-up to evaluate for McCune Albright Syndrome. While primarily idiopathic, we discuss the associated dermatologic conditions that should be considered in the differential diagnosis, including partial congenital adrenal hyperplasia, Carney Complex, Cushing Syndrome and others when presented with a patient with precocious puberty.

Keywords: Precocious puberty; Clinical syndromes; Endocrine findings

Introduction

Precocious puberty is infrequently reported in dermatology literature. In fact, the overall incidence of sexual precocity is estimated to be about 1:10,000 with a female-to-male ratio of nearly 10:1 [1]. Precocious puberty is defined as the onset of breast or pubic hair development before 8 years of age in girls and the onset of testicular development of more than 3 ml before 9 years of age in boys. In recent years, evidence suggests that normal puberty in the USA and Europe is occurring earlier. In 1999 the Paediatric Endocrine Society proposed lowering the age limit for precocious puberty to be less than 7 years old in white girls and less than 6 years old in African-American girls. Some argue that adapting the new limit will result in missed cases of precocious puberty and loss of height potential for children between 6 and 8 years [2]. Given the controversy, clinicians should consider testing for precocious puberty when managing patients in this age range. While 90-95% is idiopathic in nature, there are many syndromes and pathological conditions which can present with precocious puberty. We reviewed the literature and present conditions which could be considered by Dermatologists when approaching the management of patients with precocious puberty.

Case Report

A 9 year old African American female presented to the Dermatology clinic for non-remitting acne since age 6 years. Her

mother reported frequent week-long episodes of inflamed papulo-nodular eruptions of the forehead, cheeks, neck and back which were disfiguring and left darkly pigmented spots. She endorsed increased linear growth and early thelarche relative to her peers, but denied menarche. On physical examination, on the face and neck there were many comedonal acneiform lesions with several inflamed papules and scattered pustules. The back and chest had no active lesions, but showed evidence of post inflammatory hyperpigmentation as well as a café au lait lesion on the back. Radiographic imaging and hormone studies revealed a bone age of 11 and an LH/FSH ratio of 3.3, respectively. Due to concern for endocrinopathy, patient was to be seen by a pediatric endocrinologist. The clinical, laboratory and advanced bone age seen radiologically suggested precocious puberty secondary to an underlying central process. This led us to a clinical diagnosis of McCune Albright Syndrome.

Discussion

Precocious puberty is the development of sex characteristics prior to normal age for pubertal development due to increased sex hormone production or exposure. Patients experience increased linear growth, somatic development, skeletal maturation as well as significant cutaneous manifestations including axillary and pubic hair development, hirsutism and androgenic acne. The associated syndromes, pathogenesis and clinical findings are discussed in Table 1 and dermatologic manifestations are illustrated in Table 1 below.

Genetic Syndrome	Pathogenesis	Clinical Manifestations
McCune Albright Syndrome	Somatic mutation in the <i>GNAS</i> gene	CAL spots, polyostic fibrous dysplasia, PP
Partial Congenital Adrenal Hyperplasia	Partial deficiency of 21- hydroxylase	Precocious puberty

Carney Complex	AD mutation in the <i>PRKAR1A</i> gene	Lentigenes and multiple neoplasias; GH-producing pituitary adenomas; and testicular Sertoli cell tumors causing precocious puberty
Peutz-Jeghers Syndrome	AD mutation in the <i>STK11/LBK1</i> gene	GI polyps, periorificial pigmentation, various cancers, SCTAT (rarely) tumors leading to precocious puberty
Neurofibromatosis 1	AD defect in the <i>NF-1</i> gene	CAL spots, neurofibromas, skeletal abnormalities, Lisch nodules, optic gliomas affecting the hypothalamus causing precocious puberty
Sanfilippo disease	AR inherited enzyme deficiency and accumulation of heparin sulfate	Delayed development, hyperactivity with aggressive behavior, sleep disorders, mild hepatosplenomegaly and precocious puberty with associated coarse hair and hirsutism
Cushing Syndrome	Adrenocortical tumors, exogenous administration	Moon facies, obesity, buffalo hump, abdominal striae, diabetes, osteoporosis, adrenal tumors causing precocious puberty
Tuberous Sclerosis	AD mutation in the <i>TSC1</i> and <i>TSC2</i> genes	White macules (Ash leaf spots), multiple hamartomas, central nervous system anomalies

Table 1: Clinical manifestations and pathogenesis of heritable syndromes associated with precocious puberty (PP).

McCune-Albright Syndrome is caused by an activating somatic mutation in the *GNAS1* gene leading to constitutive ligand free activation of cellular function showing mosaic distribution with high variability of organ involvement and degree of severity. The diagnosis should be considered when at least two of the following clinical features are present: Café-Au-Lait (CAL) spots, polyostic fibrous dysplasia and endocrine abnormalities, typically precocious puberty.

The CAL spots are seen in 50% of patients affecting areas with bony prominences such as the forehead, nuchal folds, thorax and sacrum. The lesions tend to be unilateral, follow a dermatomal distribution and stop sharply at the midline with jagged borders. Interestingly, the CAL spots are often said to resemble the “Coast of Maine” in appearance. Polyostic fibrous dysplasia leads to fibrosis of the bone marrow causing brittle deformed bones. More specifically, a Shepherd crook deformity of the proximal femur is characteristic. Some recent studies report diffuse scarring alopecia showing histological features of fibrous dysplasia. [3]

Congenital adrenal hyperplasia is caused by an inherited 21-hydroxylase deficiency. With complete deficiency, patients are diagnosed as infants due to urogenital abnormalities including clitoral enlargement, rugated and partially fused labia majora, and a urogenital sinus. In partial deficiency, girls can develop normally until puberty when there are increased levels of androgenic hormones causing precocious puberty with associated acne, hirsutism, and axillary and pubic hair growth. Of note, when menstrual irregularities and infertility are present, polycystic ovarian syndrome should be considered [4].

Carney Complex is an autosomal dominant syndrome caused by mutations in the *PRKAR1A* gene characterized by lentigenes and multiple neoplasias, including: myxomas of the skin, heart and breast; psammomatous melanotic schwannomas; epithelioid blue nevi of skin and mucosae; growth hormone-producing pituitary adenomas; and testicular Sertoli cell tumors. The lentigenes occur on the face specifically involving the eyelids, vermilion border, cheeks and ears. Pituitary adenomas as well as the testicular tumors can cause sexual precocity [5].

Peutz-Jeghers Syndrome (PJS) is an autosomal dominant syndrome caused by mutations in the *STK11/LBK1* gene characterized by both gastrointestinal polyps and periorificial pigmentation. Characteristic pigmentation resembling lentigenes is seen mostly on the lips and oral mucosa. The polyps are hamartomas and benign in nature. However, PJS patients are reported to have between a 47-93% of developing any cancer before the age of 65 [6]. Common cancers reported in the literature are cancers of the small intestines, stomach, pancreas, esophagus, colon, lung, breast, ovaries, uterus and gall bladder. A distinct type of ovarian tumor, called the sex cord tumor with annular tubules (SCTAT) is found primarily in patients with PJS and has been noted to be a possible cause of precocious puberty if it occurs in prepubertal children [7].

Neurofibromatosis 1 is an autosomal dominant syndrome caused by a gene defect in *NF-1* causing café au lait macules having a “coast of California” appearance with smooth borders. Cutaneous neurofibromas, plexiform neurofibromas, and axillary or inguinal freckling are other characteristic features. Associated skeletal abnormalities include sphenoid wing dysplasia as well as pseudoarthrosis, scoliosis, and thinning of the long bone. Ophthalmologic involvement includes optic nerve gliomas (15% of children) and iris hamartomas (Lisch nodules). Precocious puberty has been described in up to 40% of patients with gliomas of the posterior chiasm due to hypothalamic involvement [8].

Mucopolysaccharidose III (Sanfilippo disease) makes up a genetically heterogeneous, but clinically similar group of 4 recognized types. Each type is caused by a different autosomal recessively inherited enzyme deficiency involved in the degradation of heparin sulfate. Patients with Sanfilippo disease are characterized by slowly progressive, severe CNS involvement with mild somatic disease. Onset occurs between 2 and 6 years of age in a previously normal child. Presenting features of Sanfilippo disease include delayed development, hyperactivity with aggressive behavior, sleep disorders, mild hepatosplenomegaly and precocious puberty with associated coarse hair and hirsutism. Severe neurologic deterioration occurs in most patients by the age of 6-10, accompanied by rapid deterioration of both social and adaptive skills [9].

Cushing Syndrome can be caused by prolonged exogenous administration of glucocorticoid hormones. In infants, it is most often caused by a functioning adrenocortical tumor. Patients often exhibit signs of hypercortisolism along with signs of hypersecretion of other steroids such as androgens, estrogens, and aldosterone. Clinical manifestations may include a rounded face with prominent cheeks and a flushed appearance (moon facies) as well as fat deposition in the nuchal area (buffalo hump). Generalized obesity is common in younger children. In children with adrenal tumors, signs of abnormal masculinization occur frequently along with precocious puberty. Growth is impaired, with length falling below the 3rd percentile, except when significant virilization produces normal or accelerated growth. Hypertension is common and may occasionally lead to heart failure. An increased susceptibility to infection may also lead to sepsis.

In older children, in addition to obesity, short stature is a common presenting feature. Purplish striae on the hips, abdomen, and thighs are common. Pubertal development may be delayed, or amenorrhea may occur in girls past menarche. Weakness, headache, and emotional lability may be prominent. Hypertension and hyperglycemia usually occur; hyperglycemia may progress to frank diabetes. Osteoporosis is common and may cause pathologic fractures [10].

Tuberous sclerosis is an autosomal dominant neurocutaneous disorder with variable clinical expression caused by mutations in the genes *TSC1* and *TSC2* leading to hamartomas of the eye, brain, kidneys, heart, and lungs. The characteristic brain lesion is a cortical tuber which can be identified with brain MRI. Common neurologic manifestations of TSC include epilepsy, cognitive impairment, and autism spectrum disorders [3]. Infants may present with infantile spasms and a hypsarrhythmic electroencephalogram pattern.

Greater than 90% of patients have cutaneous manifestations, including the typical hypomelanotic or ash leaf macules on the trunk and extremities, which accentuate with a Wood lamp examination. Additionally, facial angiofibromas develop between 4 and 6 years of age and appear as tiny red papules over the nose and cheeks. They enlarge, coalesce, and develop a fleshy appearance over time. A shagreen patch is also characteristic of TSC and consists of a roughened, raised lesion with an orange-peel consistency located in the lumbosacral region. During adolescence or later, small fibromas may form around the nails

in 15-20% of the TSC patients. While endocrine findings are rare, precocious puberty and hypothyroidism have been associated with the disease [11].

Conclusion

In summary, this case highlights the diagnosis and considerations when presented with a patient with precocious puberty. Although primarily idiopathic, this case underscores the importance of increased awareness among dermatologists of the various rare inherited conditions and their striking dermatologic findings that are associated with precocious puberty.

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