Carney Complex	AD mutation in the *PRKAR1A* gene	Lentigenes and multiple neoplasias; GH-producing pituitary adenomas; and testicular Sertoli cell tumors causing precocious puberty
Peutz-Jeghers Syndrome	AD mutation in the *STK11/LBK1* gene	GI polyps, periorificial pigmentation, various cancers, SCTAT (rarely) tumors leading to precocious puberty
Neurofibromatosis 1	AD defect in the *NF-1* 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 ulfate	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 *TSC1* and *TSC2* 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 *GNAS*1 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 boarders. 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 lentigines 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 lentigines 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 lentigines 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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