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Precocious Pseudopuberty Due to an Autonomous Ovarian Follicular Cyst

			
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ABSTRACT

A 7-year-old, phenotypically female child was referred to paediatric endocrinology consultation for premature thelarche. We found elevated oestrogen levels and failure of gonadotropin response to GnRH stimulation, and abdominal ultrasound showed autonomous ovarian cyst as the cause of peripheral precocious puberty.



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INTRODUCTION

Precocious puberty (PP) is defined as the development of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. Addressing PP involves classifying it into two subtypes: central precocious puberty (CPP), which is gonadotropin-dependent and peripheral precocious puberty (PPP), which is gonadotropin-independent. Central precocious puberty can be differentiated from peripheral type by discordant/incomplete pubertal development, GnRH/GnRHa stimulation test and imaging studies.

Diagnostic assessment includes an anamnesis and a detailed physical examination and additional tests, such as hormone tests (testosterone, 17- β -oestradiol, dehydroepiandrosterone sulphate [DHEA-S], androstenedione and 17-hydroxyprogesterone [17-OH-progesterone], β -HCG, free thyroxine [free T4] and thyroid-stimulating hormone [TSH]) and imaging tests (hand-wrist radiograph to determine bone age, pelvic or testicular and abdominal ultrasound and cranial MRI). Finally, in the presence of strong clinical suspicion, genetic testing should be performed.

CASE 1

Girl referred to paediatric endocrinology consultation at the age of 7 years with suspected precocious puberty. Antenatal, perinatal, and developmental history was unremarkable. She presented with appropriate psychomotor development for her age and her height and weight development. Her height and weight measured in the 75 percentile and 50 percentile, respectively. Development of secondary sexual characteristics was observed two weeks before, with the appearance of breast budding and pigmentation of the areola and labia majora; the pubertal stage was B3PH1 according to Tanner and Whitehouse. There were no bony deformities, *café-au-lait spots*, or signs of virilization. Her abdomen was soft, non-tender with no obvious mass palpable or ascites. She had no headache or visual complaints and did not demonstrate any neurological signs; physical examination was unremarkable.

The patient had normal blood counts and liver and kidney function tests. Laboratory tests revealed serum estradiol level elevated (80 pg/ml, prepubertal <20 pg/ml) with a suppressed FSH (<0.30 IU/L) and LH levels (0.08 UI/L). 17-OH-progesterone, DHEA-S, delta-4-androstenedione, free T4, TSH, adrenocorticotrophic hormone, cortisol (morning level) and prolactin levels were normal for her age. The LH/RH test showed a prepubertal response

(peak LH 1.2 mU/mL; peak FSH 2.5 mU/mL, LH/FSH ratio <1). Tumor markers including β -HCG, CEA, and AFP were negative.

The patient's bone age was appropriate for her chronological age. Pelvic ultrasound demonstrated the presence of a lesion (35 cm in maximum diameter) affecting the left ovary. Abdominal MRI confirmed the US findings of a unilocular functional cyst in the left ovary (33 cm in maximum diameter), thin walled, homogeneous content and without septa or solid component (Figure 2). Right ovary was normal. Uterus, measured 6.3 \times 2 \times 1.5 cms, was anteverted and had an endometrial thickness of 3.5 mm. Subsequent testing of her brain MRI was normal.



Figure 1. Magnetic resonance imaging and gross examination of the ovarian cyst.

Isosexual precocity due to estrogen-secreting ovarian cyst diagnosis was made. Laparoscopic cystectomy was performed, and histologic analysis confirmed the diagnosis of a functional follicular cyst. Genetic testing of peripheral blood revealed a 46, XX karyotype. Postoperative course was uneventful, and her breast size regressed. One month post surgery, estradiol and decreased to normal values; and ultrasound pelvic examination showed absence of pelvic masses.

DISCUSSION

Two types of PP are recognized: central precocious puberty (CPP) and peripheral precocious puberty (PPP). CPP is caused by early activation of the hypothalamus-pituitary-gonadal axis. It is usually idiopathic but secondary causes include tumors, infections, congenital defects, and radiation or injury to the brain. The sexual maturation is always complete and isosexual. Significantly advanced bone age (>2 SD), elevated (pubertal level) estrogen, basal and GnRH stimulated gonadotropin levels (predominant LH response) suggests CPP¹.

PPP does not involve the HPG axis and it is caused by release of estrogen or testosterone from abnormal organs and causes include gonadal tumor. Peripheral or gonadotropin independent precocity constitutes less than 20% of precocity cases. Causes of isosexual peripheral precocity in girls include ovarian follicular cyst, estrogen-secreting adrenal or ovarian tumors (GCT, sex-cord tumor, and estrogenizing Sertoli-Leydig cell tumors), and environmental exposure to compounds with estrogenic activity, severe untreated primary hypothyroidism, and McCune–Albright syndrome. Ovarian tumors are uncommon during childhood and are rare causes of precocity. Epithelial cell tumors ($>70\%$), germ cell tumors (20%), and sex cord–stromal tumors (8%) are the 3 main types. Maturation is most of the times incomplete/discordant with only one type of secondary sexual characteristic developing early. In most cases of PPP bone age may not be significantly (>2 SD) advanced owing to shorter duration of symptoms. Highly elevated oestrogen levels with low basal and GnRH stimulated gonadotropin levels suggests PPP.

Autonomous ovarian cysts are rare in prepubertal girls. Millar et al reported that ovarian cysts are found in prepubertal girls with a frequency of 2% to 5%². The presenting complaints in patients with ovarian masses are non-specific, making diagnosis difficult. Acute or chronic abdominal pain and abdominopelvic mass are the most common initial symptoms. Sometimes, the clinical course of these cysts is unpredictable due to episodes of hyperestrogenism typical of MAS ovarian hyperfunction, and we can find endocrine signs (pseudo-precocious puberty, signs of virilization, vaginal secretions, irregular uterine bleeding). Furthermore, autonomous ovarian cysts may be one symptom of McCune-Albright syndrome.

In this case, rapid onset of pubertal development and elevated estradiol levels was indicative of an organic condition as the cause of PP. The laboratory study showed high levels of

oestradiol, with suppressed FSH and LH levels and, GnRH-stimulation test results were compatible with pseudo precocious puberty. The pelvic ultrasound examination revealed a unilateral ovarian cyst. Magnetic resonance study showed no adrenal mass. The source of sex hormones was then localized to autonomous estradiol production from ovarian cyst.

US is the imaging modality of choice in cases of ovarian masses in children, particularly for the initial workup. Millar et al. reported that observations of small, unilocular ovarian cysts of less than 1 cm in diameter in prepubertal girls are clinically insignificant, whereas ovarian cysts associated with precocious pseudopuberty are generally larger than 2 cm in diameter².

CT scan and MRI are useful in cases of undefined mass if malignancy is suspected and before any surgery. They give additional information about the nature of the tumor and the presence of pelvic and para-aortic lymph nodes and, therefore, increases the accuracy of the diagnosis of ovarian malignancy. The evaluation of serum tumor markers, even if these are often non-specific, is very important for the differential diagnosis in pediatric ovarian masses³. Ovarian tumors, including granulosa cell tumors, are the least common cause of precocious puberty but should be differentiated from autonomous ovarian cysts, owing to their poor prognosis.

Benign ovarian cysts should be managed conservatively if the child is asymptomatic on follow up. Since spontaneous regression of pubertal signs could be seen after a few weeks with complete resolution of the ovarian cysts and endocrinological parameters returning to normal after a few months, laparotomy and ovariectomy could be avoided⁴. In persistent and recurrent large ovarian cysts with sustained estrogen hypersecretion and relevant clinical disturbances (increased linear growth and bone age maturation, vaginal bleeding and psychological disturbances) treatment is mostly necessary. Also, surgery may be required for large ovarian cysts (>20 mL) because of the risk of adnexal torsion⁵. Since most of these masses are benign, operation should be designed to optimize future fertility, and laparoscopy minimizes surgical aggression. Aromatase inhibitors are used in the management of persistent cyst. Therapy with a GnRH agonist, however, may become necessary in the case of transformation from precocious pseudopuberty to central precocious puberty after recurrences of the ovarian cysts.

CONCLUSION

Autonomous ovarian cyst causing isosexual precocious puberty in a 7-year-old girl is reported. Complete excision of the tumor led to normalization of hormonal levels and regression of secondary sexual characteristics.

In conclusion, precocious pseudopuberty in girls may be due to autonomous ovarian cysts. Therefore, all prepubertal girls with ovarian cysts should undergo careful physical examination to rule out the signs of increased hormone production associated with central precocious or pseudo precocious puberty.

Abbreviations:

AFP: Alpha-fetoprotein.

CEA: Carcinoembryonic antigen.

CPP: central precocious puberty.

FSH: Follicle stimulating hormone.

GnRH stimulation test: Gonadotropin releasing hormone stimulation test.

LH: Luteinizing Hormone

MAS: McCune-Albright síndrome.

MRI: Magnetic resonance imaging.

PPP: peripheral precocious puberty.

Conflicts of interest: The author have no conflicts of interest to declare.

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