Precocious Puberty: A Case Report

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Abstract

Background
Puberty is a transitional period in children with acceleration of growth and development of secondary sexual characteristics. When this period appears before the age of 8 to 9 years in children, it is called precocious puberty. Depending on the primary source of the hormonal production, precocious puberty may be classified as central (gonadotropin dependent or true) or peripheral (gonadotropin independent or precocious pseudo-puberty).

Case presentation
We herein report a case of precocious puberty in a 7.5-year-old girl who has shown early sign of secondary sexual development. Patients complained pain on her nipple, her breasts began to grow in size, and changes in her body odour, but had no complaints about her pubic hair growth and any vaginal discharge. Laboratory findings shown high level in fertility hormones and level of bone age is equal to 10-year-old girl. Patient then had begun to receive monthly therapy of Leuprolide.

Conclusion
Detailed history taking on chronological order of thelarche, pubarche, menarche, and adrenarche, followed by assessment on family history, nutritional history, child developmental history, medication history, and neurological complaints should be done in order to diagnose precocious puberty. Physical examination and other examination of bone age determination, Luteinizing Hormone and Follicle-Stimulating Hormone level, and pelvic ultrasound are essentials in defining the diagnosis and treatment. Leuprolide is indicated for Central Precocious Puberty patient who have advanced bone age at the time of initial evaluation. As a clinician, it is necessary to diagnose precocious puberty as soon as possible to have good prognosis for the patient.

Keywords: case report, children, gonadotropins, precocious puberty

Background
Puberty is a complex transitional period in children that includes growth acceleration and the development of secondary sexual characteristics. Precocious puberty is defined by the onset of secondary sexual characteristics before the age of 8 year in females and 9 year in males. It is a very challenging to diagnose precocious puberty as the differential diagnoses vary from benign variants to serious conditions such as malignancy.

It is stated that the precocious puberty is divided into 2 categories, the first one is caused by central problems which is gonadotropin dependent, or true precocious puberty, and the second one is peripheral problems which is gonadotropinindependent, or precocious pseudo-puberty. The central precocious puberty (CPP) is always isosexual and stems from hypothalamic-pituitary-gonadal activation with ensuing sex hormone secretion and progressive sexual maturation. Whereas in peripheral precocious puberty (PPP), the sexual characteristics may be isosexual or heterosexual (contrasexual). Some of the secondary sex characters tends to appear in peripheral precocious puberty, but there is no activation of the normal hypothalamic-pituitary-gonadal interplays.

According to the first epidemiologic study from a Danish national registry, about 0.2% of females had some form of precocious puberty (CPP, PPP, or benign variants),

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while males had less than 0.05%. Females outnumbered boys by about 20 to 23 per 10,000 girls compared to less than 5 per 10,000 boys. In Indonesia, the prevalence of precocious puberty is estimated about 1 case per 5,000 children up to 1 case per 10,000 children, with female outnumbers male. Studies in precocious puberty have been mentioned more frequent recently in pediatric endocrinology clinics than they were 20 to 30 years ago. These studies have a range of etiology and clinical manifestations, and each requires a unique therapy approach.

The clinical presentation is usually consistent with early pubertal development. Breast development in females and increased testicular volume (greater than 4 mL) in males are the first clinical signs. Other signs and symptoms including increased linear growth, acne, muscular changes, changes in body odour, and the development of pubic and axillary hair. The first step of diagnosis is to determine whether pubertal development is starting earlier than it should be. Precocious pubertal timing is crucial, resulting in a child sexually mature at an emotionally and socially inappropriate age, thus leading to risk-taking behaviours as sexual relations and substance use. Genetics plays a significant role in CPP; however, environmental factors such as obesity and adverse childhood experiences may influence pubertal development. Since it is crucial to timely diagnose precocious puberty, all general practitioners should have sufficient knowledge on how to make the working diagnosis of precocious puberty and when to refer the suspected patients. To add the body of knowledge on this topic, we presented a case study of precocious puberty in secondary hospital in Indonesia.

Case presentation
A 7.5-year-old girl presented to the pediatrics polyclinic of Unggul Karsa Medika Hospital, Bandung, West Java, Indonesia with the primary complaint of nipple pain since she was 6 years old. The pain intensified when the nipples were touched. The patient's mother stated that the patient's breasts began to grow in size. Patient’s body odour was started to change also. There was no growth of axillary or pubic hair, and no complaints of vaginal discharge. According to the patient's mother, the patient is taller and bigger than her classmates. Other complaints such as fever, convulsions, headaches, vision problems, coughing, vomiting, or abdominal pain were not present.

From history taking, we found that she had typhoid fever 3 years old and was hospitalized. She rarely ate junk food and prefers home-cooked meals. Protein consumption such as beef, pork, and chicken was uncommon. Consumption of processed food such as snacks and crisps was uncommon also. She consumed multivitamin supplements regularly, but no other medications were taken. There was no allergic history both from the patient and her family. There is no similar complaints were reported in family history. The patients’ mother had her menarche when she was 12 years old.

Neonatal history of the patient was reported that she was born prematurely via caesarean section, weighs 2,700 grams, lengths 50 cm, was healthy and normal in the neonatal period. She had all of her mandatory immunizations. Her milestone was as such: she could sit at 6 months, stand at 10 months, walk at 12 months, talk at 12 months, and read and write at 5 years old. There was no concern about her development until present. She was breastfed until two months old, but started from 2 months old, she got formula milk daily. She was given complementary food at the age of 6 months.

From the physical examination, all was normal except that her breasts had begun to develop and there was no axillary or pubic hair to be found. The patient was then advised to do laboratory examinations, abdominal ultrasound, and bone age analysis. The results shown Follicle-Stimulating Hormone (FSH) of 1.53 IU/L and Luteinizing Hormone (LH) of 1.29 IU/L. Estradiol value was 13.13 pg/mL. Abdominal ultrasound found that ratio fundus to cervix in uterus was 1 to 1.5 per 1 with size of uterus was 4.09 mL, suggestive of precocious puberty. Bone age analysis stated that her bone age was according to the age of 10-year-old girl. With these examinations, we conclude that the patient had precocious puberty. The patient then was referred to tertiary hospital to had hormonal therapy, which was Leuprolide injected intramuscularly with dose 3.75 mg once a month.

Discussion and Conclusion
Puberty is a normal physiological process of during which children develop secondary sex characteristics, experience growth acceleration, and achieve bone maturation and reproductive competence. Puberty results from the activation and maturation of the hypothalamic-pituitary-gonadal (HPG) axis. In girls, pubertal development begins with thelarche, followed by growth spurt, pubarche and menarche. Whereas in boys, pubertal development begins with testicular enlargement, followed by pubarche and a peak growth spurt.

Puberty starts with a steady increase in pulsatile release of gonadotropin-releasing hormone (GnRH) from GnRH neurons, where are located in the preoptic area and infundibular nucleus of the hypothalamus.
There are many neurotransmitters which regulate the GnRH neuron secretory pattern, with excitatory or inhibitory effects on GnRH secretion. The GnRH neurons are in a quiescent state regulated by an inhibitory network of neurotransmitters, mainly γ-Aminobutyric Acid (GABA) and Makorin Ring Finger Protein 3 (MKRN3) during childhood. At the onset of puberty, the excitatory system network is augmented, mainly by glutamate and kisspeptin, while the inhibitory system deteriorates in its activities. The HPG axis then becomes dormant until its subsequent activation in adolescence. Pulsatile release of gonadotropin-releasing hormone (GnRH) will stimulate the secretion of follicle stimulating hormone (FSH) and luteinizing hormone (LH) from the anterior pituitary gland. FSH and LH then initiate spermatogenesis and the release of testosterone in males, and oogenesis and the release of estradiol in the females. Activation of the gonads is known as gonadarche.

It is important for clinicians to be familiar with the terminology of pubertal progression. Precocious Thelarche is the development of breasts without other signs of puberty in the setting of normal growth and normal skeletal maturation, which is a response to estrogen. Pubarche is the development of pubic hair in response to androgens. Adrenarche is an activation of adrenal axis, resulting in increased secretion of androgens from adrenal glands, including Dehydroepiandrosterone Sulphate (DHEA-S). Premature Adrenarche is the onset of adrenal androgen production refers to isolated adult body odour and/or body hair (pubic and/or axillary) with or without the emergence of acne. Premature Adrenarche is more common in overweight girls and those with a history of having been born small for gestational age. Premature Menarche is described as isolated vaginal bleeding in a girl who has no other signs of pubertal development, normal growth and normal skeletal maturation. Pelvic ultrasound examination typically reveals a pre-pubertal uterus and ovaries with no evidence for infection or foreign body.

In our patient, we could find premature thelarche and changes of body odour, which is associated with increased secretion of DHEA-S. However, we could not find any body hair both pubic and axillary hair and no acne. Menarche was also had not happened in our patient. CPP may be considered in girls who have progressive breast development and who cross percentiles upward on the linear growth chart. Thus, CPP diagnosis in our patient could be reasoned. However, since CPP is occasionally inherited from the parents, such as menarche in the mother at 10 years or younger and growth spurt in the father before 12 years of age, we had not found any suggestion that our patient’s condition is inherited. Her mother had her menarche in 12 years of age. The pattern of inheritance of CPP is usually autosomal-dominant.

The most common cause of CPP is idiopathic, in >90% of affected girls and 25-60% of affected boys. Kisspeptin, the peptide product of KISS1 gene and its receptor, the G-protein 54 (GPR54) signaling complex are essential to the pubertal activation of GnRH neurons. An increase in kisspeptin signaling caused by enhanced expression of KISS1 and GPR54 genes contributes to the activation of HPG axis. Therefore, gain-of-function mutations in both genes could induce precocious puberty. Loss-of-function mutations in the makorin ring finger protein 3 (MKRN3) gene were also shown to lead to idiopathic CPP.

Other exogenous factors such as iatrogenic and neurological disturbances should be asked by the clinicians. The use of sex steroids, including ingestion of oral contraceptive pills or exposure to transdermal estrogen creams or testosterone gels. Any central nervous system (CNS) symptoms, including severe frequent headaches or recent visual deficits, and a history of disorders associated with CPP such as brain tumor, meningitis, CNS trauma, cranial irradiation, hypoxic-ischemic injury, histiociytosis, and neurofibromatosis should be asked also. In our case, there were no history of using sex steroids or any CNS symptoms.

Interactions between genetic, endocrine, and environmental factors are essential in pubertal timing. Nutritional status is considered one of the most important factors involved in pubertal development and it was estimated to explain as much as 25% of the variation in the timing of puberty. The use of formula feeding may induce overweight development and predisposition to childhood obesity through increased Insulin Growth Factor-1 (IGF-1) and consequent enhanced sex steroid production. Our patient was given formula feeding from 2 months old. Thus, could increase risk for precocious puberty. High-energy diet could induce higher levels of leptin, IGF-1 activation, adrenal androgen overproduction, and increased conversion of androgens to estrogens, so increasing risk for precocious puberty. Protein intake could lead to adipo-sity rebound before pubertal onset and IGF-1 secretion. Fat intake has direct effect on steroidogenesis and mammary gland development, and has indirect effect through induction of low-grade hypothalamic inflammation. Carbohydrate intake could induce rapid increase in insulin concentration in high-glycemic-index diets, resulting in increased availability of sex hormones and IGF-1. All could increase risk for precocious puberty.
Physical examination in girls focuses on the Tanner stage of breast development and determination of whether there are supporting signs of estrogen effect, including maturation of the nipples and areolae and a mucous vaginal discharge. In boys, change in voice, acne, or facial hair are the signs of significant androgen effect. Pubic hair, apocrine odor, and axillary hair in both boys and girls are typically related to adrenal androgen production, though are not reliable signs of CPP.

Diagnostic evaluation of suspected CPP will include a bone age determination, baseline laboratory testing of FSH, LH, and either estradiol or testosterone. An LH of >0.3 IU/L is the most reliable screening test for CPP. If it is <0.3 and CPP is still suspected, stimulation test with GnRH analogue may be necessary. In our case, LH was 1.29 IU/L, thus CPP could be diagnosed. Pelvic ultrasonography may help to exclude ovarian tumour or large ovarian cyst. Ultrasound also could measure whether ovarian and uterine volumes are increased or not. In our case, uterine volume was 4.09 mL, consistent with study from Lee, et al that found uterine volume of least 3.30 mL was the most predictive parameter for CPP.

Treatment with GnRH analogues such as leuprolide can be given via injection at monthly or 3-month intervals. Leuprolide is a synthetic decapeptide that binds to the GnRH receptors in the pituitary with more stability and longer half-life than natural GnRH. The mechanism of action is suppression of the episodic release of GnRH from the hypothalamus and downregulation of the pituitary GnRH receptors resulting in suppression of the HPG axis. This treatment is recommended in CPP patients who have advanced bone age at the time of initial evaluation (less than 12.5 years in girls or less than 14 years in boys) for the purpose of height preservation. Leuprolide is not recommended for treatment of CPP in patients with markedly advanced bone age of more than 12.5 years in girls or more than 14 years in boys at the time of diagnosis since there are no beneficial out-comes in of HPG axis suppression or height preservation beyond these ages. Leuprolide should be discontinued when the patient is at the appropriate age to resume normal pubertal development or when their calculated predicted final adult height is at about their target height or their bone age is more than 12.5 years in girls or more than 14 years in boys. The goal of treatment includes preservation of linear growth potential, suppression of menses, shrinkage or softening of the glandular breast tissue or the testes. Slowing of growth velocity to <7 cm/year is the goal. In our patient, Leuprolide was given due to advanced bone age less than 12.5 years (10 years of age).

Untreated precocious puberty usually leads to short stature and has significant emotional and behavioral damages. Studies stated that children experiencing precocious puberty are at risk of engaging in high-risk behaviors: substance abuse, conduct issues, social isolation, truancy, and multiple sexual partners. They also experiencing some kind of peer pressure and self-image concerns. However, most of these problems resolved by early adulthood.

Earlier onset of treatment is associated with greater success in order to preserve final adult height. Factors such as advancement of bone change, age at which precocious puberty initiated, the timing of initiation, and duration of treatment are very crucial. HPG axis will return to normal after the cessation of the therapy, and these children will have a normal progression of puberty. The prognosis of PPP varies depending on the cause.

Conclusion
The case presented in this article provides good study of diagnosing precocious puberty in girls. Detailed history taking on the chief complaint must direct clinicians to have full chronological order of thelarche, pubarche, menarche, and adrenarche. Assessment on family history, nutritional history, child developmental history, medication history, and neurological complaints should be done in order to get full risk factors of precocious puberty. Physical examination will reveal the stage of precocious puberty of the patient. Bone age determination, LH and FSH level, and pelvic ultrasound are essentials in defining the diagnosis and treatment. Leuprolide, a GnRH analogue is indicated for CPP patient who have advanced bone age at the time of initial evaluation. As a clinician, especially general practitioner, it is necessary to have a good body of knowledge in precocious puberty in order to screen the incidence of this disorder and can refer it as soon as possible to get good prognosis for the patient.
List of abbreviations
CPP - Central Precocious Puberty
PPP - Peripheral Precocious Puberty
FSH - Follicle-Stimulating Hormone
LH - Luteinizing Hormone
HPG - Hypothalamic-Pituitary-Gonadal
GnRH - Gonadotropin-releasing hormone
GABA - γ-Aminobutyric Acid
MKRN3 - Makorin Ring Finger Protein 3 gene
DHEA-S - Dehydroepiandrosterone Sulphate
GPR54 - G-protein 54 gene
KISS1 - Kisspeptin gene
CNS - Central Nervous System
IGF-1 - Insulin Growth Factor-1

Declarations
Ethics approval and consent to participate
Informed consent from the patient has been obtained before the study.

Consent for publication
Consent for publication regarding patient data has been obtained before the study.
All the patient identity has been kept secret.

Availability of data and materials
Not Applicable

Competing interests
The authors declare that they have no competing interests.

Funding
There is no funding from third party for this case report to be completed.

Acknowledgements
We acknowledge the help from Unggul Karsa Medika Hospital where this case was found and could be reported in the form of case report.

Received : 28 September 2022
Accepted : 13 October 2022
Published Online : 17 October 2022

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