Archives of the Balkan Medical Union
vol. 54, no. 4, pp. 776-780
December 2019


CASE REPORT

# PRECOCIOUS PUBERTY: HOW ABOUT THE ACCELERATED BONE MATURATION?

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*Received 10 Oct 2019, Accepted 13 Nov 2019*
https://doi.org/10.31688/ABMU.2019.54.4.26

## Abstract

**Introduction.** Precocious puberty is a common endocrine disorder in pediatric patients, leading to important changes in growth patterns.
**Case presentation.** We present the case of a patient with precocious puberty and accelerated bone maturation, evaluated in several medical centers. A 9-year-and-11-month-old female patient was evaluated for premature thelarche, adrenarche and menarche starting at the age of 7. On clinical examination, height was 143 cm, 0.9 SD above the age and sex median, with 37.91% excess weight. She also presented with acne, cervical posterior acanthosis nigricans, hirsutism and Tanner puberty development stage B3/P4. The endocrine profile showed pubertal values for FSH (Follicle-Stimulating Hormone), LH (Luteinizing Hormone) and estradiol, before and after the Diphereline test, hyperprolactinemia (of 38.6 ng/mL, normal: 2-18.9 ng/mL) and high levels of 17-OH Progesterone (of 2.60 ng/mL, normal: 0.2-0.9 ng/mL). The Synactene® test excluded 21-hydroxylase

## Résumé

**Puberté précoce: qu'en est-il de la maturation osseuse accélérée?**

**Introduction.** La puberté précoce est un trouble endocrinien courant chez les patients pédiatriques, entraînant des changements importants dans les schémas de croissance.
**Présentation du cas.** Nous présentons le cas d'un patient atteint de puberté précoce et de maturation osseuse accélérée, évalué dans plusieurs centres médicaux. Une patiente âgée de 9 ans et de 11 mois a été évaluée pour une prématurité de la thélarche, la ménarche et l'adrénarche à partir de 7 ans. À l'examen clinique, la taille était de 143 cm, dont 0,9 DS au-dessus de la médiane de 37,91 % surpoids. Elle a également présenté l'acné, l'acanthosis nigricans postérieur du col utérin, l'hirsutisme et le stade de développement B3 / P4 de la puberté de Tanner. Le profil endocrinien montrait des valeurs pubertaires pour la FSH (hormone folliculo-stimulante), la LH

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deficiency. Knee X-rays showed a tendency for premature growth plate fusion and bone age advancement of 3.1 years. Gynecological examination and pelvic ultrasound showed normal ovarian morphology and volume, according to chronological age and a 17-mm endometrium. Hypothalamic-pituitary MRI (Magnetic Resonance Imaging) excluded the presence of a local lesion.

**Conclusions.** In the absence of therapeutic intervention, accelerated skeletal development due to precocious puberty initially leads to high stature compared to the patient's age group, followed by premature closure of the growth plates and low final height.

**Keywords:** precocious puberty, bone age, Diphereline.

(hormone lutéinisante) et l'estradiol, avant et après le test Diphereline, l'hyperprolactinémie (de 38,6 ng/ml, la normale: 2-18,9 ng/ml) et des taux élevés de 17-OH progestérone (de 2,60 ng / ml, normale: 0,2-0,9 ng / ml). Le test au Synactène excluait le déficit en 21-hydroxylase. La radiographie du genou a montré une tendance à la fusion prématurée du plateau de croissance et à la progression de l'âge osseux de 3,1 ans. L'examen gynécologique et l'échographie pelvienne ont montré une morphologie et un volume ovariens normaux, en fonction de l'âge chronologique et d'un endomètre de 17 mm. L'IRM hypothalamo-hypophysaire (imagerie par résonance magnétique) exclut la présence d'une lésion locale.

**Conclusions.** En l'absence d'intervention thérapeutique, le développement squelettique accéléré dû à la puberté précoce entraîne initialement une taille élevée par rapport au groupe d'âge du patient, suivi de la fermeture prématurée des plaques de croissance et d'une hauteur finale réduite.

**Mots-clés:** puberté précoce, âge osseux, Diphéreline.

## Introduction

Premature activation of the hypothalamic-pituitary-gonadal axis due to precocious puberty leads to important changes in the growth plates. Precocious puberty is one of the most common endocrine disorders seen in children[1].

Puberty is a very complex physiological stage of sexual development, which can be influenced by multiple factors such as genetics, nutrition, environment and economy. In the pubertal development process, individuals acquire secondary sex characteristics and the capacity for reproduction[2]. Puberty onset in girls is marked by the development of breasts. The appearance of pubic hair in both sexes can be encountered before, at the same time or after the onset of the pubertal process[3].

Puberty normally begins between the ages of 8 years and 13 years in girls, 9 years and 14 years in boys, respectively. Lately, a decrease in the age of puberty onset has been observed, due to an optimal state of health, proper nutrition and better socioeconomic status[4]. In girls, precocious puberty is defined as the development of secondary sex characteristics before the age of 8 years. Precocious puberty can be classified based upon the underlying pathologic process into the gonadotropin-dependent form, known as central precocious puberty and the gonadotropin-independent form, also called precocious pseudopuberty[5]. We present the case of a patient with central precocious puberty and accelerated bone maturation, who was evaluated in several medical centers.

## Case presentation

A 9-year-and-11-month-old female patient, without significant past medical history, was admitted for endocrine assessment, presenting with hirsutism, acne, regular menstrual cycles and weight gain. Her medical history revealed the occurrence of thelarche, pubarche, adrenarche and menarche at the age of 7 years. Clinical examination showed a height of 143 cm, 0.9 SD above the age and sex median, target height based on mid parental height of 159 cm, weight of 49 kg with 37.91% excess weight, acne lesions on the face and the posterior thoracic wall, cervical posterior acanthosis nigricans, hirsutism with a Ferriman-Gallwey score of 24, puberty development stage B3/P4, blood pressure of 105/60 mmHg, heart rate of 82 beats/min. The endocrine profile showed pubertal values for FSH, LH and estradiol, before and after the Diphereline test, hyperprolactinemia (of 38.6 ng/mL, normal: 2-18.9 ng/mL) and high 17-OH Progesterone levels (of 2.60 ng/mL, normal: 0.2-0.9 ng/mL). The Synacthen test excluded 21 hydroxylase deficiency (Table 1). Thyroid function tests revealed subclinical hypothyroidism in the absence of significant findings on thyroid ultrasound. No pathological changes in biochemical parameters were found. Non-dominant hand radiography showed bone age advancement of 3.1 years, while knee

**Table 1.** The endocrine and biochemical parameters of a young girl diagnosed with precocious puberty.

| *Parameters* | *Values* | *Normal limits* | *Units* |
|---|---|---|---|
| Estradiol | 68.3 | <30 | pg/mL |
| FSH | 4.70 | 0.9-7.83 | mU/mL |
| LH | 17.02 | 0.2-1.67 | U/L |
| Estradiol* | 114.3 | <60 | pg/mL |
| LH** | 180.2 | <6 | U/L |
| PRL | 38.6 | 2-18.9 | ng/mL |
| Testosterone | 0.35 | 0.1-0.5 | ng/mL |
| 17OH progesterone | 2.60 | 0.2-0.9 | ng/mL |
| 17OH progesterone after Synacthen test | 4.72 | <10 | ng/mL |
| DHEA-S | 2.12 | 0.15-2.15 | µg/mL |
| Serum Cortisol | 22.7 | 6-23 | µg/dL |
| TSH | 2.27 | 0.36-5.5 | µU/mL |
| FT4 | 0.69 | 0.72-1.3 | ng/dL |
| Anti-TPO | 0.74 | < 10 | U/mL |
| Anti-Tg | <1 | <4 | U/mL |
| Alkaline phosphatase | 251 | 51-332 | U/L |
| Serum glucose | 88 | 60-100 | mg/dL |
| Cholesterol | 193 | < 200 | mg/dL |
| Triglycerides | 145 | < 150 | mg/dL |

Legend. FSH= Follicle-Stimulating Hormone; LH= Luteinizing hormone; PRL= Prolactin; 17OH progesterone= 17 hydroxyprogesterone; DHEA-S= Dehydroepiandrosterone sulfate; TSH= Thyroid Stimulating Hormone; FT4= Free Thyroxine; Anti-TPO = Anti-thyroid peroxidase antibodies; Anti-Tg= antithyroglobulin antibodies; Estradiol value 4 hours after 100 µg intravenous Diphereline. ** LH value 24 hours after 100 µg intravenous Diphereline.

radiography showed a tendency for premature growth plate fusion (Figure 1 and Figure 2). Gynecological examination and pelvic ultrasound revealed normal ovarian volume and morphology according to the chronological age and an endometrium of 17 mm. Hypothalamic-pituitary MRI excluded the presence of a local lesion. Thyroid replacement therapy and dopaminergic agonists were prescribed. In addition, the patient was started on a hypocaloric diet.

## Discussion

Central precocious puberty occurs as a result of premature hypothalamic-pituitary-gonadal axis activation. The responsible factors can be various cerebral lesions, either congenital or acquired, but usually the cause cannot be established. The diagnosis and optimal management of this condition often represent a challenge for the endocrinologist[6].

The age of puberty onset has important biological and psychosocial consequences and can affect the individual's health in the long run[7]. The main problem related to precocious puberty is short adult height, despite initial accelerated growth, due to premature fusion of the growth plates. There are also psychosocial implications. Studies have shown that precocious puberty is related to health issues later in life. There have been associations with obesity, type 2 diabetes, coronary artery disease, hypertension, stroke, hormone-dependent cancers due to high exposure to estrogens[8-10].

On presentation, careful clinical examination of the child is needed in order to identify a cause for the condition, including signs of a possible genetic disease that can be associated with precocious puberty[11]. The diagnosis requires hormone tests, radiography of the non-dominant hand and knees, pelvic ultrasound and cerebral MRI[12,13]. Also, the presence of a pituitary incidentaloma might be positive but this does not represent a major clue for etiological diagnosis, due to the high frequency in general population[14-16].

The gold standard treatment includes long-acting GnRH agonists, which suppress pituitary LH and FSH release due to the desensitization of gonadotropic cells. This can lead to the stabilization or regression of pubertal development, decreasing bone age advancement[17-22]. Because of a delayed referral to the endocrinologist, in the present case imaging tests of the hand and knees showed advanced bone age and a tendency for premature growth plate fusion. In

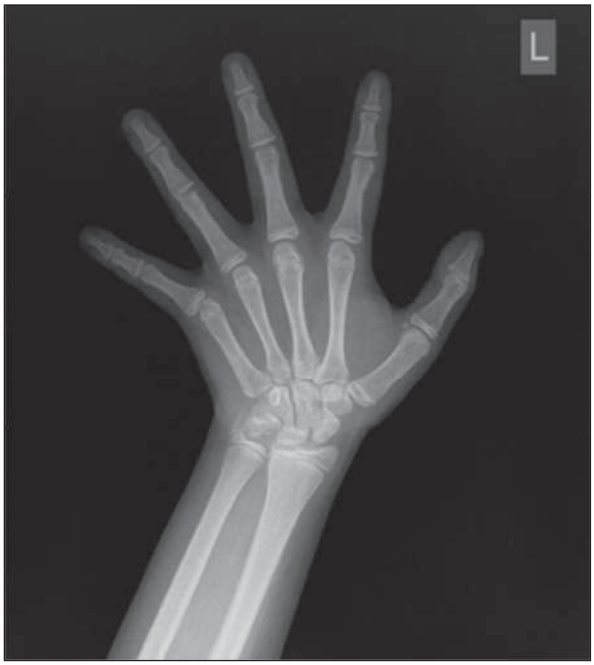


**Figure 1.** Non-dominant hand radiography of a 9-year-and-11-month-old girl diagnosed with idiopathic precocious puberty: bone age advancement of 3.1 years.

this situation, we considered treatment with GnRH agonists to be inappropriate. At presentation, the height of the patient was within the normal range for age and sex, but the X-ray findings suggest that height velocity will decrease due to the 3-year advance in bone age, leading to short final stature. The brain MRI found no lesions responsible for precocious puberty, placing the patient in the idiopathic precocious puberty group.

## Conclusions

Precocious puberty is a common endocrine disorder seen in pediatric patients. The early diagnosis and identification of the cause are essential in choosing the appropriate treatment and limiting the consequences of the disease, not only on final height, but also on the metabolic level.

### Compliance with Ethics Requirements:

*„The authors declare no conflict of interest regarding this article"*

*"The authors declare that all the procedures and experiments of this study respect the ethical standards in the Helsinki Declaration of 1975, as revised in 2008(5), as well as the national law. Informed consent was obtained from the patient included in the study"*

*„No funding for this study"*

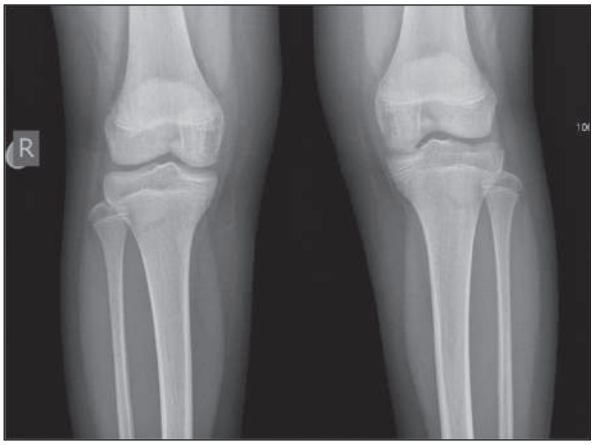


**Figure 2.** Bilateral knee radiography of a 9-year-and-11-month-old girl diagnosed with idiopathic precocious puberty: growth plates with a tendency to close

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