DOI: https://doi.org/10.17816/PED12171-77

PRECOCIOUS PUBERTY IN GIRLS: A CLINICAL CASE OF IDIOPATHIC CENTRAL PRECOCIOUS PUBERTY

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For citation: Lagno OV, Turkunova ME, Bashnina EB. Precocious puberty in girls: a clinical case of idiopathic central precocious puberty. *Pediatrician (St. Petersburg).* 2021;12(1):71-77. https://doi.org/10.17816/PED12171-77

Received: 19.12.2020 Revised: 15.01.2021 Accepted: 19.02.2021

Central precocious puberty occupies an important place in the practice of a pediatric endocrinologist. If the patient reveals signs of premature sexual development, the diagnostic search is aimed at eliminating the tumor origin of both false (peripheral) and gonadotropin-dependent, or central, precocious puberty, as well as gonadotropin-independent forms of premature sexual development. Oncological alertness is important in the work of not only a pediatric endocrinologist, but also a pediatrician. In the treatment of all non-tumor forms of central precocious puberty, drugs of the group of analogues of gonadotropin-releasing hormone are used, which allows to stop the progression of sexual development, reduce the rate of bone maturation and, thereby, increase the final growth of the child. The most common idiopathic variant of central precocious puberty. The article presents a clinical case of observing a patient with an idiopathic variant of central premature sexual development during therapy with a drug from the group of analogues of gonadotropin releasing hormone of prolonged action. The classical course of the idiopathic variant of central precocious puberty with typical diagnostic difficulties in the onset of the disease, good compensation against the background of therapy with a drug from the group of agonists of gonadotropin-releasing hormone and normal puberty 6–12 months after cancellation of the therapy is demonstrated. The latter is explained by the proven reversibility of the effects of this group of drugs. The description of this clinical case, in the authors' opinion, should be of interest to doctors at the local pediatricians and pediatricians working in the medical care departments for children in educational institutions.

Keywords: precocious puberty; idiopathic central precocious puberty; GnRH agonist treatment; triptorelin.

ПРЕЖДЕВРЕМЕННОЕ ПОЛОВОЕ РАЗВИТИЕ У ДЕВОЧЕК: КЛИНИЧЕСКИЙ СЛУЧАЙ ИСТИННОГО ИДИОПАТИЧЕСКОГО ПРЕЖДЕВРЕМЕННОГО ПОЛОВОГО РАЗВИТИЯ

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Для цитирования: Лагно О.В., Туркунова М.Е., Башнина Е.Б. Преждевременное половое развитие у девочек: клинический случай истинного идиопатического преждевременного полового развития // Педиатр. – 2021. – Т. 12. – № 1. – С. 71–77. https://doi.org/10.17816/PED12171-77

Поступила: 19.12.2020 Одобрена: 15.01.2021 Принята к печати: 19.02.2021

Преждевременное половое развитие занимает важное место в практике детского эндокринолога. При выявлении у пациента признаков преждевременного полового развития диагностический поиск направлен на исключение опухолевого генеза как ложного (периферического), так и истинного, или центрального, преждевременного полового развития, а также гонадотропин-независимых форм преждевременного полового развития. Онкологическая настороженность важна в работе не только детского эндокринолога, но и врача-педиатра. В лечении пациентов

со всеми неопухолевыми формами центрального преждевременного полового развития используют препараты группы аналогов гонадотропин-рилизинг-гормона, что позволяет остановить прогрессирование полового развития, снизить темпы костного созревания и, тем самым, увеличить конечный рост ребенка. Наиболее часто встречается идиопатический вариант центрального преждевременного полового развития. В статье представлено клиническое наблюдение пациентки с идиопатическим вариантом центрального преждевременного полового развития. Изложено классическое течение идиопатического варианта центрального преждевременного полового развития с типичными сложностями диагностики в дебюте заболевания, хорошей компенсацией на фоне терапии препаратом из группы агонистов гонадотропин-рилизинг-гормона и нормальным половым созреванием через 6–12 мес. после отмены терапии. Описание данного клинического случая может быть интересно педиатрам и эндокринологам.

Ключевые слова: преждевременное половое развитие; идиопатическое центральное преждевременное половое развитие; лечение агонистами гонадотропин-рилизинг-гормона; трипторелин.

Precocious puberty (PP) in girls is diagnosed when all or some secondary sexual characteristics appear before eight years old. According to the current classification, there are true PP, false PP, and incomplete PP (premature thelarche, premature adrenarche, and premature menarche). The cause of true PP is the premature activation of the hypothalamic-pituitary (HT-P) system, which may be due to tumors of the central nervous system (CNS), pineal gland, organic non-neoplastic lesions of the CNS, irradiation of the brain, pathology of migration of gonadotropin-releasing hormone-secreting neurons, genetic syndromes such as Russell-Silver syndrome, or neurofibromatosis type I. Untreated primary hypothyroidism and late treatment with an excess of sex hormones in false PP also lead to true PP [16]. If the above causal factors are excluded, true idiopathic PP is diagnosed in the patient with laboratory-proven HT-P activation of ovarian function. True PP can be complete if the patient has developed all secondary sexual characteristics (enlargement of the mammary glands, hair growth in the pubic area, armpits, and the onset of menarche). True PP is considered incomplete if not all secondary sexual characteristics have appeared yet.

False PP is caused by hypersecretion of sex hormones (androgens or estrogens) without activating the HT-P system. Autonomous hypersecretion of estrogens can be caused by a tumor of the ovaries or adrenal glands or exogenous administration of estrogens. In this case, PP develops in an isosexual manner. The development of heterosexual false PP causes an excess of androgens caused by androgen-producing tumors of the ovaries or adrenal glands or impaired adrenal steroidogenesis due to various enzymatic defects, as in congenital suprarenal cortex hyperplasia (CSCH) [15].

Until a specific time, generally, before reaching the "pubertal" bone age, the McCune–Albright–Braitsev syndrome belongs to the variant of false PP. The pathology is caused by the autonomous functioning of ovarian follicular cysts. Estrogen production is associated with the pre-pubertal structure of luteinizing hormone (LH) secretion with no response to gonadotropin-releasing hormone (GRH). Later, usually with the onset of ovulatory cycles, gonadotropin-dependent puberty occurs [6, 7, 16]. McCune–Albright–Braitsev syndrome is a rare genetic disorder based on somatic mutations in the GNAS gene. Clinical signs of the disease include light brown spots with clear boundaries, localized usually on the hips, back, lower back, chest, and in places of bone deformities, and fibrous dysplasia and hyperfunction of the endocrine glands [13]. McCune–Albright–Braitsev syndrome and persistent follicular cysts in girls are classified as a separate group of gonadotropin-independent PP caused by the activation of steroid-secreting elements of the genital glands without the involvement of gonadotropins [8].

In most cases, both true and false PP, there is a significant acceleration of bone age. In the absence of timely diagnosis and therapy in patients, the growth zones are rapidly closed, which results in the formation of short stature in adulthood [4, 8, 12].

Separately, it is required to highlight such incomplete forms of PP, as premature thelarche and premature adrenarche. Premature thelarche is represented by a unilateral or bilateral development of the mammary glands that starts in infancy, more often at two years. It is not accompanied by other symptoms of sexual development. There can rarely be the development of mammillae, vaginal mucosa thickening, and estrogen-induced enlargement of the uterus. This condition is usually benign and is associated with the secretion of follicle-stimulating hormone (FSH) and the development of antral follicles to a greater extent than in the pre-pubertal control group. Unstimulated and GRH-stimulated plasma LH levels correspond to the values typical for the pre-pubertal period [6].

The diagnosis of premature adrenarche is established after ruling out false and true PP.

The term adrenarche implies a physiological process that starts in healthy individuals at the age of 6–8 years, as a rule, two years or more before activating the HT-P system and an increase in gonadotropin secretion. At this age, the secretion of dehydroepiandrosterone and androstenedione, synthesized in the reticular zone of the adrenal cortex, increases, which is not clinically manifested, except as a minor increase in the growth rate and increased secretion of apocrine sweat glands. In some children, an increase in the activity of 17,20-lyase and 17-α-hydroxylase results in the premature appearance of pubarche (hair growth in the pubic region) and terminal hair in the axillary region, which is premature adrenarche. In the international literature, this term is interpreted as excessive adrenarche [10]. Most girls with premature adrenarche have a moderate acceleration of bone age, and the level of 17-hydroxyprogesterone (17-OHP) may exceed the norm in children in the pre-pubertal period, which necessitates differential diagnostics of premature adrenarche and nonclassical form of CSCH [1, 9, 14, 17]. Despite the increase in growth rate and bone age, the final height with premature adrenarche does not change. However, the probability of polycystic ovary syndrome in adulthood is increased [6, 19]. According to Russian authors, the hormonal marker of premature adrenarche is an increased level of androstenedione [2].

According to the Federal Clinical Guidelines for the Management of Patients with PP, PP is diagnosed in stages. At stage 1, it is required to establish the presence of PP, to identify a group of incomplete forms (premature thelarche and premature adrenarche). At stage 2, it is necessary to establish a nosological variant in patients with confirmed PP to determine the therapeutic approach [8].

Modern diagnostic standards require a short-acting GRH stimulation test. This test enables the differentiation of gonadotropin-dependent forms of PP from gonadotropin-independent and isolated thelarche in girls. In treating all variants of gonadotropin-dependent PP, including true idiopathic PP, drugs from the group of GRH analogs with prolonged action are effectively used, which desensitize the pituitary gland to the stimulating effect of its gonadotropin-releasing hormone. The drugs from this group, such as Diphereline 3.75 mg, Diphereline 11.25 mg, Decapeptil depot 3.75 mg with triptorelin as an active ingredient, and Lyukrin 3.75 mg and Lyukrin depot 11.25 mg (active ingredient leuprorelin), are registered in Russia.

After magnetic resonance imaging (MRI) of the brain and pituitary gland, organic tumor causes of PP and hamartoma of the hypothalamic region can be ruled out [5]. It should be noted that hypothalamic hamartoma is not a tumor but is a congenital ectopia of hypothalamic tissue and causes PP in 70% of cases. In addition to PP, hamartomas of hypothalamic localization are accompanied by neurological disorders and behavioral disorders and can cause diabetes insipidus [8].

The drug of choice in the treatment of true idiopathic PP was triptorelin 3.75 mg, which suppresses effectively the secretion of gonadotropins and sex steroid hormones, which, in turn, stops the development of secondary sexual characteristics and leads in some patients to their regression, contributes to the regulation of patient behavior. Long-term therapy with triptorelin effectively regulates bone age in patients and ensures optimal stature in children with true PP [3, 8, 18].

The criteria for the efficiency of therapy with drugs from the group of long-acting analogs of GRH, which include triptorelin (3.75 mg), can be considered as a decrease in the growth rate to the age norm, the absence of progression of sexual development, or regression of secondary sexual characteristics, an increase in bone age by no more than one year within the current year. Low basal levels of LH and estradiol in girls may be considered the efficiency criterion initially elevated levels of these hormones. With the low efficiency, 3–6 months after the start of treatment, the test with short-acting triptorelin is repeated with anticipated LH release of no more than 4 U/L during the test [8].

As an example of a differential diagnostic algorithm, selection of treatment, and further follow-up monitoring of premature sexual development in girls, we present a clinical case of a patient with true idiopathic PP. The results of follow-up monitoring of patients with true PP in St. Petersburg revealed that the idiopathic variant accounts for 50% of cases with this pathology [11].

Patient P., 7.5 years old, was admitted for examination at the endocrine department of the clinic due to the premature appearance and progression of secondary sexual characteristics.

At the time of hospitalization, the case history revealed an increase in mammary glands in the girl since the age of 4.5 years old, which at the outpatient stage was regarded as an incomplete form of PP, namely isolated thelarche. At the age of 6.5 years old, due to a gradual increase in the mammary glands, an ultrasound scan of the pelvic organs was performed and showed the size of the uterus and ovaries corresponding to 11 years. Hormonal examination revealed basal LH 1.5 mMu/ml,

FSH 5.26 mMu/ml, and estradiol 49.6 pmol/l, corresponding to stage II of puberty on the Tanner scale. Hospitalization in the pediatric endocrine department was recommended. With the appearance and progression of pubarche, the patient was immediately hospitalized.

Upon admission, height was 134 cm (+2.5 SDS), body weight was 30.5 kg (+0.25 SDS weight for height). Body mass index (BMI) was 16.9 kg/m^2 (±1 SDS). Sexual formula on the Tanner scale was AI PII–III MaIII Me (–). The growth rate was 14 cm per year. Bone age corresponded to 9.5 years. Ultrasound examination (US) of the pelvic organs (uterus 4.5 × 1.8 × 1.5 cm; left ovary 2.0–1.4–1.9 cm, 4–5 follicles up to 3 mm; right ovary 2.0–1.4–1.8 cm, 3–5 follicles up to 4 mm), which corresponded to 11 years. Hormonal examination showed the basal level of LH hormones 3.3 mIU/ml, FSH 4.9 mIU/ml, and estradiol 62 pmol/l, 17-OHP 0.85 ng/ml. There were no indications for an adrenocorticotropic hormone test to rule out the nonclassical form of CSCH based on the 17-OHP value obtained. Ultrasound of the adrenal glands revealed no pathology.

The standard for diagnosing true PP is a short-acting GRH test [8, 15]. After a stimulation diagnostic test (0.1 mg of triptorelin was injected subcutaneously), the maximum increase in the levels of the hormones under study was LH 67.9 mMe/ml and FSH 21.1 mMe/ml.

MRI of the brain and pituitary gland showed no MRI data on the presence of space-occupying paraplasms in the chiasmo-sellar region. True idiopathic PP was diagnosed in the patient.

In a patient with clinical manifestations of PP, the diagnosis of true idiopathic premature puberty was established at 7.5 years, and therapy with a drug from the group of long-acting GRH analogs triptorelin (3.75 mg) was started according to the scheme at a dose of 3.75 mg intramuscularly one time in 28 days. The conditions for treatment with a long-acting triptorelin drug are continuity of therapy, calendaring, and adherence to the injection regimen. The patient did not violate the recommended triptorelin injection regimen.

Subsequently, the patient was examined on an outpatient basis. The case follow-up showed that the patient stopped the progression of secondary sexual characteristics; with palpation of the mammary glands, the gland tissue was slightly increased, mainly due to the fatty component. On day 26, after administration of triptorelin (3.75 mg), LH level was 0.2 mIU/ml, FSH was 0.6 mIU/ml, which indicated a positive effect of therapy. Ultrasound of the pelvic organs showed that the size of the uterus and ovaries corresponded to the age of 9 years. In the first year of treatment, the growth rate was 6.5 cm. The progression of bone age slowed down, which after one year of therapy corresponded to 10 years.

In the subsequent second year of therapy, the patient's growth rate was 4.5 cm per year. Bone age corresponded to 10.5 years. Sexual formula on the Tanner scale was AI PIII Ma II–III Me (–). Since androgenization has increased, and the growth rate over the past six months of follow-up was 1 cm, it was decided to cancel hormonal therapy. At the time of completion of treatment, the girl was nine years old and nine months old. Her physical development was assessed as high and harmonious, with a height of 146 cm (+2.5 SDS), a bodyweight of 40.5 kg (+0.9 SDS weight for height), and a BMI of 18.9 kg/m^2 (+1.2 SDS).

One year after the end of therapy with triptorelin, an ultrasound scan of the pelvic organs revealed the size of the uterus and ovaries corresponding to 9 years. X-ray data of her hands showed the bone age corresponding to 11.5 years. Her sex hormone levels (LH 5.45 mIU/ml, FSH 7.16 mIU/ml, and estradiol 49.5 pmol/L) corresponded to stage III of puberty by the Tanner scale (AIII PIV Ma III Me (–)). Her growth rate was 8 cm/year. Menarche was registered 15 months after discontinuation of therapy.

A control medical examination, which was performed 30 months after completion of therapy with triptorelin (3.75 mg), when the girl was 12 years old and three months, showed that the patient's menstrual function became regular 10–12 months after menarche. The levels of sex hormones taken on day 5 of the menstrual cycle were 2.61 mIU/ml of LH, 6.9 mIU/ml of FSH, and 26.1 pmol/l of estradiol. Ultrasound of the pelvic organs showed that the size of the uterus and ovaries corresponded to 12.5 years; single follicles with a diameter of up to 5 mm were located in the ovaries along the periphery. The physical development of the patient was assessed as above average and harmonious. Her height was 160 (+1.6 SDS), and her body weight was 50.5 kg (+0.1 SDS). A feminine physique was formed. Sexual development was AIII PIV Ma IV Me (+). Regular menstruation after 28–30 days corresponded to stage IV on the Tanner scale.

The initiation of therapy with a long-acting triptorelin drug in our patient enabled us to block the progression of the gonadarche and slow down the early closure of bone growth zones. The duration of therapy was two years, three months. At the end of therapy, the child's height was two years ahead

of the average height by age and balanced with bone age. After completion of therapy, gradual development of secondary sexual characteristics was registered. Menarche appeared 15 months after completion of therapy with triptorelin (3.75 mg). Then, 2.5 years after the completion of therapy, the patient's physical and sexual development and the results of hormonal and instrumental research methods corresponded to her passport age.

CONCLUSION

Thus, true idiopathic PP was diagnosed in the patient with the onset of PP at 4.5 years of age and the progression of the disease from 6.5 years of age. Timely diagnostics and efficient and safe therapy contributed to the normalization of the physiological parameters of growth and sexual development of the child. The latter is explained by the proven reversibility of a group of drugs of GRH agonists in treating central forms of PP, including true idiopathic PP. The concern is that some other forms of gonadotropin-dependent PP at the onset start to manifest in the same way as true idiopathic PP. Unfortunately, there is faster disease progression, the closure of growth zones, and the risk of short stature in adulthood. Pediatricians, in the course of scheduled follow-up monitoring, may notice the period of initial manifestations of PP in children, manifested by an increase in mammary glands in girls, an increase in the size of testicles in boys, and a pronounced acceleration of the growth rate, which is very important for early disease diagnosis.

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