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THE OUTCOMES OF TRUE PREMATURE SEXUAL DEVELOPMENT IN GIRLS AFTER COMPLETION OF CYCLIC SUPPRESSIVE THERAPY

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ABSTRACT. ***Introduction.*** In the practice of a pediatric endocrinologist, there is a well-developed algorithm of actions to assess the causes and decide on treatment options for a patient with true premature sexual development (iPPR). After eliminating the volumetric formation of the central nervous system, cyclic suppressive therapy with triptorelin is prescribed. ***The purpose*** of this study was to study the formation of puberty in girls after the end of iPPR therapy with triptorelin. To achieve this goal, tasks were set, including the analysis of medical records of girls with iPPR who had previously received triptorelin therapy; conducting an online questionnaire of patients on the formation of their puberty period with an assessment of growth, determining the time of menstruation after drug withdrawal; studying family history concerning the start of puberty in relatives. A literary search on the topic of the study revealed that in recent years information has appeared about the genetic basis of iPPR. ***The results*** of the study showed that the duration of cyclic suppressive therapy with triptorelin iPPR affects the timing of the appearance of the first menstruation in patients. With therapy for more than 5 years, menstruation occurs later than in patients using the drug for a shorter period of time. In most patients, an important goal of therapy was achieved — the prevention of accelerated bone differentiation with premature closure of growth zones and stunting. With delayed initiation of therapy, stunting could not be prevented. ***Conclusions.*** Clinical manifestations of sexual development in patients after completion of treatment with triptorelin prove the reversibility of its antigonadotropic effect. The formation of the menstrual cycle after discontinuation of treatment occurs later in those who have used the drug for more than 5 years. Timely initiation of iPPR treatment helps to avoid stunting in most patients. To verify the genesis of iPPR, it is advisable to conduct a molecular genetic study, given the high frequency of familial forms of this disease. It is important to know the long-term results of the use of suppressive therapy of iPPR, its possible impact on the reproductive period of patients' lives.

KEYWORDS: *true premature sexual development, outcomes of suppressive cyclic therapy with triptorelin, puberty formation, molecular genetic studies*

ИСХОДЫ ИСТИННОГО ПРЕЖДЕВРЕМЕННОГО ПОЛОВОГО РАЗВИТИЯ У ДЕВОЧЕК ПОСЛЕ ЗАВЕРШЕНИЯ ЦИКЛИЧЕСКОЙ СУПРЕССИВНОЙ ТЕРАПИИ

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РЕЗЮМЕ. ***Введение.*** В практике детского эндокринолога для оценки причин и принятия решения о вариантах лечения пациента с истинным преждевременным половым развитием (иППР) существует отработанный алгоритм действий. После исключения объемного образования центральной нервной системы назначают циклическую супрессивную терапию трипторелином. ***Целью*** данного исследования было изучение становления пубертатного периода у девочек после окончания терапии иППР трипторелином. Для достижения цели были поставлены задачи, включающие анализ медицинских карт девочек с иППР, ранее получавших терапию трипторелином; проведение онлайн-анкетирования пациенток по вопросам становления у них пубертатного периода с оценкой роста, определением времени появления менструации после отмены препарата, изучение семейного анамнеза, касающегося старта пубертата у родственников. Литературный поиск по теме исследования выявил, что в последние годы появилась информация о генетических основах иППР. ***Результаты*** проведенного исследования, показали, что длительность циклической супрессивной терапии трипторелином иППР влияет на сроки появления первой менструации у пациенток. При терапии более 5 лет менструации наступают позже, чем у пациенток, применяющих препарат более короткий период. У большинства пациенток была достигнута важная цель терапии — предупреждение ускоренной дифференцировки костей с преждевременным закрытием зон роста и низкорослостью. При отсроченном начале терапии предотвратить низкорослость не удалось. ***Выводы.*** Клинические проявления полового развития у пациенток после завершения лечения трипторелином доказывают обратимость его антигонадотропного действия. Становление менструального цикла после отмены лечения наступает позже у тех, кто применял препарат более 5 лет. Своевременное начало лечения иППР помогает избежать низкорослости у большинства пациенток. Для верификации генеза иППР целесообразно проведение молекулярно-генетического исследования, учитывая высокую частоту семейных форм этого заболевания. Важно знать долгосрочные результаты использования супрессивной терапии иППР, возможное ее влияние на репродуктивный период жизни пациенток.

КЛЮЧЕВЫЕ СЛОВА: *истинное преждевременное половое развитие, исходы супрессивной циклической терапии трипторелином, становление пубертатного периода, молекулярно-генетические исследования*

INTRODUCTION

The incidence of gonadotropin-dependent, or true precocious puberty (TPP) ranges from 1:5000 to 8:10,000 in the pediatric population. TPP is characterized with the appearance of secondary sexual characteristics in girls before the age of 8 years and in boys before the age of 9. Girls are significantly more often affected [1]. If organic pathology of the central nervous system (tumors, hamartomas, residual-organic lesions of the central nervous system (CNS)), as well as TPP stimulated by excessive sex steroids in congenital hyperplasia of the adrenal cortex is excluded, the cause of premature activation of the hypothalamic-pituitary-gonadal axis (HPGA) in 50 to 90% of cases remains unclear and is designated as idiopathic precocious sexual development [2].

A number of population studies have noted a correlation between the age of onset of puberty in children and their parents. Moreover, the timing of sexual development features (including menarche) is more consistent in monozygotic twins. The genetic regulation of HPGA involved in puberty has been actively studied [3–5].

In recent decades, there has been significant progress in the study of hereditary variants of TPP, which is primarily due to the expanding capabilities of molecular genetics. Emerging publications show that 25–27.5% of cases of gonadotropin-dependent TPP are familial forms of the disease, which have a monogenic nature [6].

Identification of genetic markers of TPP has shown that mutations in the *KISS1*, *KISS1R*, *MKRN3*, and *DLK1* genes are most often associated with premature activation of HPGA in childhood [2, 7].

The neuropeptide kisspeptin (KISS1 gene, cytogenetic localization of the gene — 1q32.1, OMIM no. 603286) is an endogenous ligand of the KISS1R receptor (GPR54 gene, cytogenetic localization — 19p13.3, OMIM no. 604161) [8].Kisspeptin binds to its receptor on hypothalamic and adeno-hypophysial neurons and stimulates the activity of these receptors. Kisspeptin is currently recognized as the most important regulator of puberty onset, sex hormone-mediated gonadotropin secretion, and fertility [9, 10].

The *MKRN3* gene is localized on the long arm of chromosome 15 (15q11.2, OMIM no. 603857) [8]. Mutations in the *MKRN3* gene are believed to be the leading mutation among familial forms of TPP. Geneticists believe that when this gene is mutated, abnormalities develop in cases when the defect is inherited in both paternal and maternal lines [11]. It is possible that *MKRN3* has a suppressive effect on gonadotropin-releasing hormone (GnRH)-secreting neurons during childhood, whereas its loss of function contributes to the activation of GnRH secretion and the premature onset of puberty [6]. Asymptomatic carriage of pathogenic variants of the gene has also been reported, confirming the possibility of incomplete penetrance [12].

TPP can be inherited by three mechanisms: autosomal dominant, autosomal recessive, and additive ones. These mechanisms depend on mutation that results in the manifestation of a certain disorder. The *MKRN3* and *DLK1* genes are characterized by an imprinting pattern of inheritance. Epigenetic modifications that alter the expression of these genes are also considered among the causes of precocious puberty [7]. *DLK1* (cytogenetic location: 14q32.2, OMIM no.176290) [8] is expressed from the father [13, 14].

Obviously, there is a special demand for genetic screening of children from families with an aggravated hereditary history of TPP.

Information about genes associated with TPP is being supplemented by other candidate genes: *MAPK8IP3* (OMIM no. 605431), *POU1F1* (OMIM no. 173110) and *NPFF1R* (cytogenetic location: 10q22.1, OMIM no. 607448) [6, 8]. *MAPK8IP3* gene is localized on the short arm of chromosome 16 (16p13) and is characterized by autosomal dominant type of inheritance. Heterozygous mutations of this gene are often associated with various variants of neurodevelopmental disorders, in 50% of cases combining with brain anomalies [15].

Both autosomal recessive and autosomal dominant types of inheritance can occur in TPP caused by a mutation of the *POU1F1* gene mapped on the short arm of chromosome 3 (3p11.2). Moreover, interaction of *POU1F1* with a number of transcription factors is necessary for targeted and selective differentiation of thyroid and gonadotropic cell lines of adenohypophysis. Therefore, pathogenic variants of *POU1F1* genes can also lead to deficiency of other adenohypophysis hormones [16].

The product of *NPFFR1* gene expression is a neuropeptide receptor that is localized on GnRH-secreting hypothalamic neurons. Aberrations in *NPFFR1* may also contribute to premature activation of HPGA.

Unfortunately, the method of genetic analysis of TPP is still in early use in our domestic clinical practice.

In case hypothalamic-sellar volumetric masses are detected, a neurosurgeon together with an endocrinologist decide whether neurosurgical intervention is necessary and appropriate.

In case of CNS neoplasms that do not require surgical treatment, as well as in all other cases of TPP, conservative therapy is indicated. The main goal of therapy for TPP is to suppress the development of secondary sexual characteristics that cause psychological discomfort and social difficulties for the child and his or her parents, as well as to normalize the rate of linear growth, slow the rate of ossification, and prevent stunting [1].

Prolonged GnRH analogs are used for the pharmacologic treatment of TPP [2]. Regular cyclic administration of luliberin agonists promotes desensitization of pituitary gonadotrophs and suppression of luteinizing hormone (LH), follicle stimulating hormone (FSH) secretion. As a result, there is a decrease in the formation of sex steroids in gonads. Such therapy is widely used in the world and has a long history (more than 30 years) [17, 18].

In the Russian Federation, the GnRH analog triptorelin has been registered and has been clinically tested. The drug is administered intramuscularly, the frequency of administration is once every 28 days. For children weighing less than 20 kg — 1.875 mg, more than 20 kg — 3.75 mg. There are prolonged analogs of GnRH in Russia. Triptorelin has a longer action, it is administered in 11.25 mg once every 12 weeks [2].

Both foreign and domestic publications have previously reported the high efficacy of this therapy by blocking the secretion of gonadotropic hormones and the progression of puberty [19–21].

In some countries, an implant with a GnRH agonist, histrelin (Supprelin) is inserted, its effect lasts for 1 year [22, 23]. However, this requires surgical intervention and regular monitoring of efficacy. After 12 months, the current implant should be removed and replaced with another to continue treatment. Permission to use this method in domestic medicine has not yet been obtained.

The question of whether the long-term use of suppressive therapy with gonadoliberins in TPP can affect puberty remains relevant for practical health care. The effects of these drugs with respect to final growth, timing of therapy completion and recovery of the hypothalamic-pituitary axis, and safety of therapy are debated.

AIM

To study pubertal maturation in girls after completion of cyclic suppressive therapy for TTP with triptorelin.

MATERIALS AND METHODS

There have been analyzed medical records of 17 girls with TPP. All girls were examined in the endocrinology department of St. Petersburg State Pediatric Medical University and received cyclic suppressive therapy with triptorelin until the age of 12 years.

All patients aged 3–8 years were diagnosed with TPP based on the characteristic clinical picture and the results of the test with a synthetic short-acting GnRH analog. After the exclusion of a volumetric mass based on the results of magnetic resonance imaging of the brain with pituitary contrasting, TPP of central genesis was considered idiopathic, and suppressive therapy with triptorelin was prescribed. The drug administration regimen was cyclic, according to the clinical recommendations that were valid at the time of treatment [2]. After the start of therapy blocking LH and FSH secretion, all patients underwent regular monitoring by an endocrinologist, including in-depth examination in an endocrinologic hospital once a year. Therapy with GnRH analogs had an effective and persistent effect on suppressing puberty: it led to a decrease in the volume of breast glands, regression of sexual characteristics, and disappearance of menstruation. In addition, the effectiveness of the therapy was evidenced by the results of ultrasound examination of the pelvic organs (uterus and ovaries volume reduction, decrease in the size and number of follicles), inhibition of bone age. LH, FSH, estradiol levels reached pre-pubertal values. It should be noted that the parents of four girls also entered puberty

early. The duration of GnRH treatment depended on the age when secondary sexual characteristics appeared and the time therapy was started. All children completed therapy at the age of 12 years.

An online questionnaire was administered to girls. It contained questions about puberty, estimated growth estimation, menstrual timing after drug withdrawal, and family history of pubertal onset in relatives. The age of the girls at the time of interview ranged from 12 years 9 months to 17 years 4 months.

Patients were divided into two groups according to the duration of triptorelin therapy: Group 1 (58.8%) received the drug for less than 5 years (from 1 year to 4 years 3 months), Group 2 (41.2%) – from 5 years and up to 7 years 10 months. The growth of the patients was analyzed according to standard deviations. Height within ±1 SDS was considered average; ±1 to ±2 SDS was considered above and below average, respectively; more than –2 SDS was considered stunted and more than +2 SDS was considered tall. The time of onset of menstruation was determined.

RESULTS

Follow-up monitoring of the patients after discontinuation of treatment indicated a gradual recovery of gonadal function, manifested by enlargement of breast glands, progression of pubic and axillary hair loss. After discontinuation of triptorelin therapy, menstruation started in 6 months in 23.5% of the patients, including 17.6% in Group 1 and 5.9% in Group 2. The onset of menstruation in the period from 6 months to 1 year after the end of treatment was noted in 52.9% of patients, including 35.3% in Group 1 and 17.6% in Group 2. Later onset of periods (1.5-2 years later) was observed in 17.6% of patients, including 5.9% in Group 1 and 11.8%

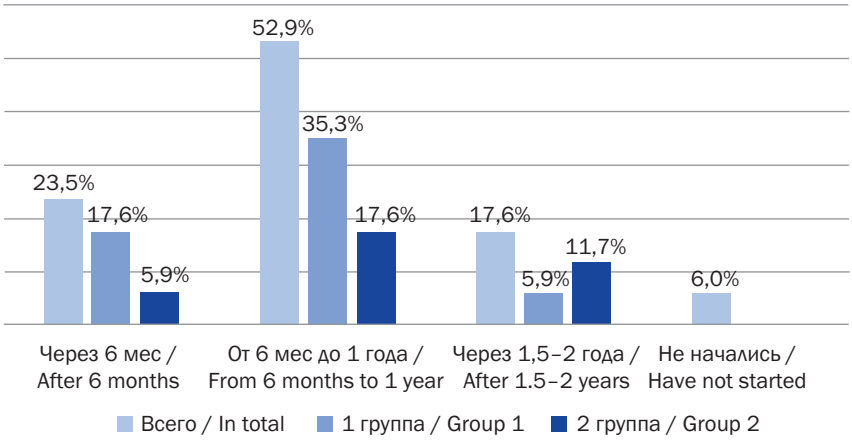

Fig. 1. The appearance of menarche depending on the duration of suppressive therapy

Рис. 1. Появление менархе в зависимости от продолжительности супрессивной терапии

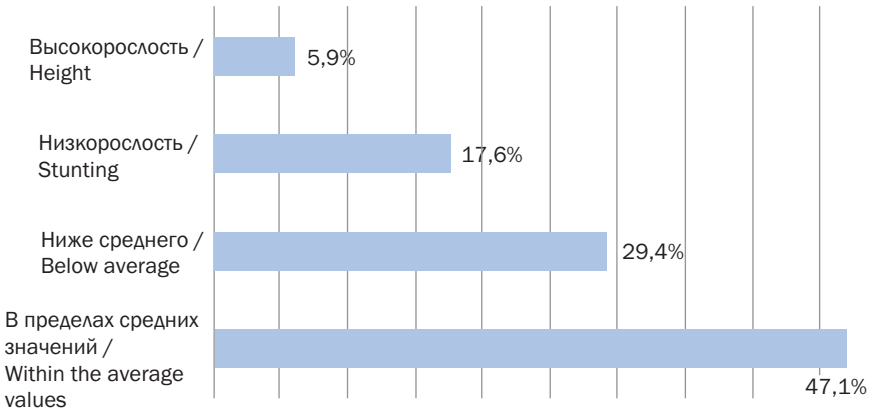

Fig. 2. Growth at the time of the survey

Рис. 2. Рост на момент анкетирования

in Group 2 (Fig. 1). One girl aged 16 years had no menstruation, which was explained by polycystic ovary syndrome (PCOS) diagnosed during the examination.

The relatively later development of menstrual function in girls who received GnRH suppressive therapy for more than 5 years (in group 2) can be associated with the fact that after longer treatment the body needs more time to restore the natural cycle of hormonal regulation.

The height of the patients at the time of the questionnaire was within average values in 47.1% of girls, below average in 29.4%, low height in 17.6%, and high height in 5.9% of patients (Fig. 2).

Girls who started triptorelin suppressive therapy within the first year of the TPP onset (64.7%) showed average growth in 54.5% of cases, below average growth in 36.4%, and stunting in 9.1% of cases. At a later start of therapy, 2-3 years after the first signs of TPP (35.3%), average height was observed in 33.3% of patients, below average — in 16.7%, stunting — in 33.3% of patients, and in one case high stature was observed (Fig. 3).

When treatment duration was less than 5 years, 30% of the patients had average height, 30% had height below average, 30% had stunting, and 10% had high stature. In case of prolonged therapy (more than 5 years), average height was registered in 71.4% of the patients in this group, below average — in 28%, stunting was not registered (Fig. 4).

Clinical peculiarities of sexual development after completion of triptorelin treatment prove reversibility of an antigonadotropic effect of triptorelin. The function of sex glands is successfully restored after the end of treatment. However, one of the observed patients aged 16 years had no menstruation, and during the examination she was diagnosed with polycystic ovary syndrome, primary amenorrhea, normogonadotropic ovarian dysfunction, normoprolactinemic variant. Further, this patient was initiated treatment with a contraceptive combined drug (estrogen+gestagen) with antiandrogenic effect by a gynecologist.

Longer-term results (ovulation, fertility) in individuals who received suppressive therapy with triptorelin in childhood have not yet been sufficiently studied due to the lack of a long follow-up period [22–24]. Nevertheless, it is important to understand the long-term outcomes of suppressive therapy and TPP. Medical literature has reported pregnancy in women treated with GnRH [25, 26].

Thus, the problem of TPP in girls is extremely important since this condition and the choice of its treatment may affect the future reproductive function of female

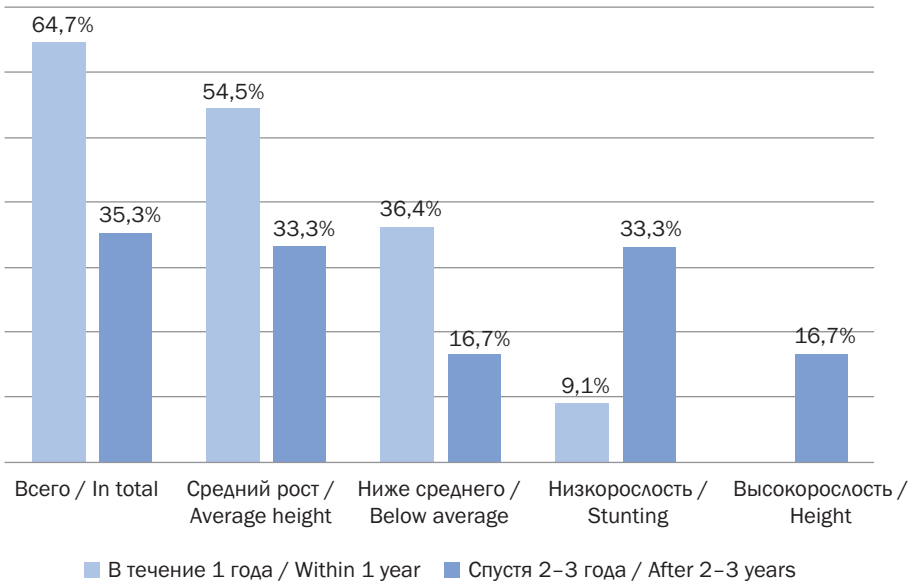

Fig. 3. The dependence of growth on the time on the initiation of therapy after the appearance of the first signs of precocious puberty

Рис. 3. Зависимость роста от времени начала терапии после появления первых признаков преждевременного полового развития

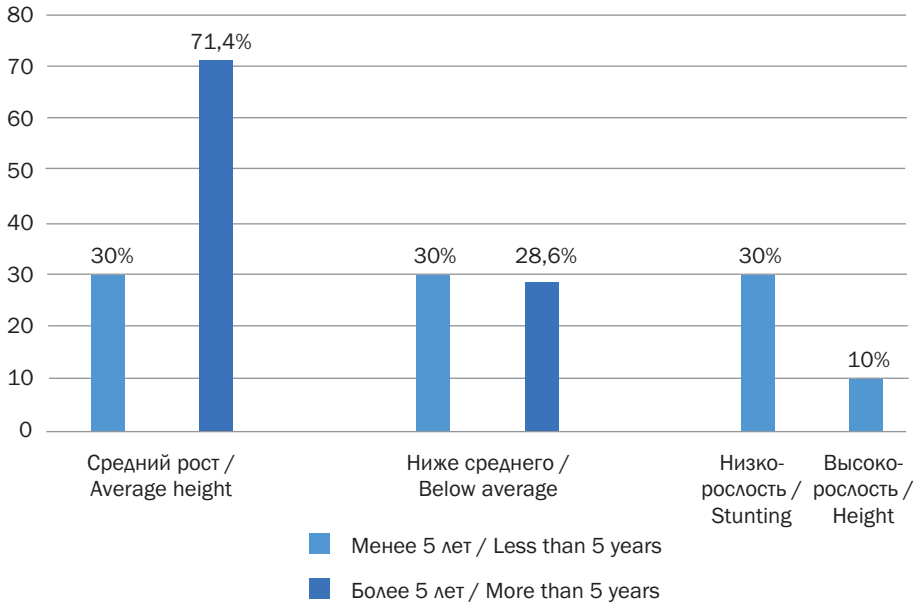

Fig. 4. The dependence of growth on the duration of treatment

Рис. 4. Зависимость роста от длительности лечения

patients. The lack of data regarding associated pathogenic genes in the examined patients with TPP necessitates further inclusion of a molecular genetic study to verify possible causes of TPP.

CONCLUSION

Clinical manifestations of sexual development in female patients after completion of triptorelin treatment prove the reversibility of an antigonadotropic effect of triptorelin. The menstrual cycle establishment occurs later after treatment withdrawal in those who used the drug for more than 5 years. Timely initiation of TPP treatment helps to avoid stunting in the majority of patients. Molecular genetic study is advisable to verify the genesis of TPP, given the high frequency of familial forms of this disease. It is important to know the long-term results of using suppressive therapy for TPP and its possible impact on the reproductive period of patients' life.

ADDITIONAL INFORMATION

Author contribution. Thereby, all authors made a substantial contribution to the conception of the study, acquisition, analysis, interpretation of data for the work, drafting and revising the article, final approval of the version to be published and agree to be accountable for all aspects of the study.

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

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Consent for publication. Written consent was obtained from legal representatives of the patients for publication of relevant medical information within the manuscript.

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Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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