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Precocious puberty in children - diagnosis, causes and treatment

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Abstract

Physiological sexual maturation begins with pulsatile gonadoliberin (GnRH) secretion by neurons in the arcuate hypothalamic nuclei. GnRH affects the synthesis and pulsatile secretion of the anterior pituitary gonadotropic hormones - LH and FSH, which through stimulation of the gonads lead to the production and secretion of sex hormones - estrogens and testosterone. Sex hormones are responsible for the development of secondary and tertiary sexual characteristics. The mechanisms

responsible for inhibiting GnRH secretion in pre-pubertal children have not been fully understood, but they are most likely the result of homeostasis prevailing between neuronal excitatory and inhibitory systems. The entire course of puberty in children is a complex process and is influenced by a wide range of environmental and individual factors. This translates into a large range of physiological age limits for the onset of puberty: in girls between 8 and 13 years of age (on average 10 years), while for boys between 9 and 14 years of age (on average 12 years).
Many factors are responsible for precocious puberty in children. The course of the disease affects both the physical and psychological sphere of the child. In order to compensate for the distant effects of this disease, it is necessary to detect symptoms early and implement effective treatment to avoid long-term complications. Emphasis should also be placed on health education to raise public awareness.

Key words: precocious puberty, puberty, children, GnRH

Introduction

Physiological sexual maturation begins with pulsatile gonadoliberin (GnRH) secretion by neurons in the arcuate hypothalamic nuclei. GnRH affects the synthesis and pulsatile secretion of the anterior pituitary gonadotropic hormones - LH and FSH, which through stimulation of the gonads lead to the production and secretion of sex hormones - estrogens and testosterone. Sex hormones are responsible for the development of secondary and tertiary sexual characteristics. In girls, secondary sexual characteristics are: vulva, vagina, uterus, fallopian tubes, while tertiary sexual characteristics include: breasts, sexual hair and body proportions. In boys, among the secondary sexual characteristics are scrotum, penis and vasa deferentia, while tertiary sexual characteristics include hair growth, a decrease in the tone of the voice, and shoulder girdle muscle development [1,2,3].
The mechanisms responsible for inhibiting GnRH secretion in pre-pubertal children have not been fully understood, but they are most likely the result of homeostasis prevailing between neuronal excitatory and inhibitory systems. The initiation of physiological maturation occurs by stimulating the kiss peptin and neurokinin B systems. These polypeptides, by interacting with specific receptors on GnRH neurons and by suppressing the inhibitory activity of the GABAergic system, lead to cyclic GnRH secretion. The entire course of puberty in children is a complex process and is influenced by a wide range of environmental and individual factors. This translates into a large range of physiological age limits for the onset of puberty: in girls between 8 and 13 years of age (on

average 10 years), while for boys between 9 and 14 years of age (on average 12 years). However, the onset of puberty at this age does not exclude the disease underlying this condition [1,2,3].

Precocious puberty (Latin Pubertas praecox) is a sex hormone-induced condition in which secondary and tertiary sexual characteristics develop before the age of 8 years in girls and 9 years of age in boys. Precocious puberty can be categorized as GnRH-dependent, GnRH-independent and benign variants.

GnRH-dependent precocious puberty (also called central, idiopathic or constitutional) occurs in response to premature activation of the hypothalamic-pituitary-gonadal axis. In contrast, GnRH independent (alleged, incomplete) precocious puberty occurs in the case of autonomic secretion of sex hormones through the adrenal glands or gonads. It can have two forms - isosexual, in which sexual development is compatible with the sex of the child, or heterosexual, when feminization in boys and virilization in girls occurs. In turn, mild variants of this disease are characterized by a lack of progression of symptoms and constitute about 50% of all cases of premature puberty [1].

Progressive precocious puberty occurs at a frequency of 1: 5000 children, with 10 times more common occurrence in girls. [4]

Clinical picture

Assessment of sexual development should be an integral part of the child's physical examination. Only through regular examinations can slight changes be identified and precocious puberty identified at its initial stage.

Symptoms of isosexual precocious puberty in girls include breast enlargement (Th> = 2), pigmentation of the nipple areola, labia and vaginal vestibule, presence of fluor pubertalis or bloody discharge, thickening, swelling and bruising of the hymen, as well as development pubic and axillary hair (> = 2) and the hip belt. In turn, in boys with isosexual precocious puberty is increased testicular volume (> = 4 ml), development of cavernous bodies, pigmentation of the penis and scrotum, development of pubic hair (> = 2) as well as weight gain and development of the shoulder girdle.

In the situation of heterosexual development of precocious puberty in girls, virilization occurs, which includes: enlargement of the clitoris, premature pubarche, lack of development of the mammary glands, hirsutism, lowering of the voice and muscularization of the figure. On the other hand, in the case of feminization, boys suffer from: lack of scrotum and penis development, eunuchoid proportions of the body, gynecomastia and high tone of voice.

For both sexes, it is also possible to distinguish common features of premature puberty, such as increased growth rate, acceleration of bone age by a minimum of 1-2 years (depending on the

child's age), low final height, abnormal body proportions, acne, oily hair, sweat odor , changes in behavior and interests, masturbation, as well as intellectual development consistent with chronological age. [1,2,3,5,6]

Diagnostics

Diagnosis of premature puberty should be started with measurements of body length and weight and its proportions, followed by comparison of our results with previous ones marked on centile grids.
Among laboratory tests, special attention should be paid to sex hormones and tumor markers, such as estradiol, testosterone, DHEAS, Ca-125, CEA, beta-hCG, AFP, anti-Mullerian hormones. Genetic testing can also be helpful. In each case of GhRH-dependent precocious puberty, an MRI of the hypothalamic-pituitary region should be performed to diagnose structural changes.[1] Ultrasound of the abdomen should be performed. In central premature puberty ultrasound may reveal enlarged ovaries, an increased uterine volume and a midline endometrial echo. [7]

Causes of precocious puberty

1. **GnRH-dependent precocious puberty**

Every case of GnRH-dependent precocious puberty will lead to development of isosexual form, both in female and male.

1.1 Functional disorders of central nervous system

Causes for precocious puberty on the basis of functional CNS disorders are most often idiopathic of unknown etiology, in which GnRH neurons are stimulated. A similar pathogenesis of the disease can be seen in a girl adopted from a developing country. In this case, socioeconomic stimuli and xenestrogens presented in the environment can also stimulate GnRH-secreting neurons. Another possibility is the activating mutation of the KISS1R gene, responsible for the stimulation of GnRH neurons with subsequent cyclic secretion of gonadoliberin.
Functional CNS disorder can also be caused by excess sex hormones in the alleged premature puberty. Excess of hormones stimulate the maturation of the hypothalamic-pituitary-gonadal axis at 11-12 years of age. Treatment leads to a decrease in sex hormones, which results in unblocking of the axis. [1,3]

1.2 Structural changes in the hypothalamic-pituitary region

Precocious puberty occurs when the neuronal pathways of the inhibiting GnRH neurons are destroyed and TGF-alpha is secreted from damaged glial cells. This process leads to the activation of GnRH neurons.

The causes of structural changes include: CNS tumors such as glioma of the optic nerves (NF1), pineal gland, ependymoma, astrocytoma and germ cell tumor. Injuries, chemo- and / or radiotherapy, encephalitis or meningitis, ischemic encephalopathy, post-stroke status and chronic granulomatous disease may also lead to structural changes. The last large set of possible causes are developmental abnormalities such as hamartoma, hydrocephalus, arachnoid glandular cyst, cerebral ventricular cyst, empty saddle syndrome, ocular-ocular dysplasia, myelomeningocele or ectopy of the posterior pituitary lobe [1,8]

2. GnRH independent precocious puberty

GnRH-independent precocious puberty are usually caused by autonomic secretion of sex hormones by the adrenal glands or gonads.

2.1 GnRH independent gonadal precocious puberty

McCune-Albright syndrome is responsible for GnRH-independent precocious puberty of gonadal origin. Post-zygomatic somatic mutation of the GNAS1 gene leads to stimulation of signal transduction of LH and FSH receptors (but also ACTH, TSH, PTH, GHRH and MSH), resulting in the isosexual form of premature puberty. Such a situation, however, rarely occurs in boys. [1]

In contrast, the form limited to the male is testotoxicosis, which arises from the germinal mutation activating the LH receptor. As a result, autonomous secretion of testosterone by Leydig cells occurs and leads to the isosexual form of premature puberty. This mutation is inherited autosomally dominant, but in the case of the female sex there are no symptoms - women are carriers.[1,2]

Precocious puberty on the basis of ovarian tumors is another option. Ovarian tumors arise from granular or Sertoli cells and lead to autonomous secretion of estradiol, resulting in development of isosexual form in girls. However, in the case of Leydig cell tumors or teratomas, the testosterone is secreted autonomously, resulting in a heterosexual form of premature puberty in girls.[1,3]

Testicular tumors are also the cause of isosexual form of precocious puberty in boys. Among all testicular tumors, leyidigioma is the most common. Autonomous secretion of testosterone by this lesion leads precocious puberty. In contrast, the heterosexual form arises most often on the basis of autonomic estradiol secretion by testicular tumor in Peutz-Jeghers syndrome. [1]

Embryonic tumors, such as: dysgerminoma, pinealoma, hepatoblastoma, chorionepithelioma may be located in the gonads, but also in the retroperitoneal and intracranial spaces. They secrete hCG with LH activity, which results in the secretion of testosterone by Leydig cells in the testes and tecal cells in the ovaries (due to the lack of FSH that stimulates aromatase - there is no secretion of estradiol by the ovaries). This leads to an isosexual form in boys. However, in the case of girls, the form depends on the activity of aromatase in the tumor - if it is present, the character is isosexual, if absent - heterosexual. [1]

Primary hypothyroidism can lead to TSH-dependent precocious puberty. High levels of TSH have FSH activity [9] and lead to secretion of estradiol in the ovaries (isosexual form), and testicular enlargement caused by hyperplasia of seminiferous tubules (partial form - lack of testosterone). [1]

2.2 GnRH independent precocious puberty with adrenal origin

The basis for the formation of GnRH-independent precocious puberty of adrenal origin is the excess secretion of ACTH, which stimulates the secretion of androsterone, DHEAS and testosterone through the reticular layer of the adrenal cortex and leads to the isosexual form of premature puberty in boys. In girls it is a heterosexual form, however, it rarely develops, because sexual development disorders are already visible in the newborn.

Congenital adrenal hyperplasia which results in 21-hydroxylase, 11-beta-hydroxylase, 3betaHSD2 deficiency is another cause. Adrenal cortical tumors such as cancer, adenoma or primary pigmentary nodular adrenal disease may also lead to precocious puberty. Glucocorticoid resistance syndrome resulting from glucocorticoid receptor gene mutation may also be responsible for precocious puberty.

In contrast, aromatase deficiency syndrome, which arises from the germinal inactivating mutation of the CYP19 gene, usually leads to pubarche praecox. [1,5]

2.3 GnRH independent precocious puberty with peripheral tissues origin

The activating CYP19 mutation results in aromatase excess syndrome, characterized by an overexpression of aromatase. Excessive aromatization of testosterone to estradiol, which occurs in the ovaries and in adipose tissue leads to the isosexual form of premature puberty in girls and gynecomastia in boys. [10]

2.4 Benign variants of precocious puberty

The distinguishing feature of benign variants of precocious puberty is the non-progressive nature of the lesions. The mild forms of premature puberty include Thelarche praecox, Adrenarche praecox and Menarche praecox.

The etiology of Thelarche praecox is not fully understood, however, it is likely that the estradiol receptor is hyperactive, which results in the development of mammary glands. In the case of Adrenarche praecox, most likely, a prematurely mature reticulated adrenal cortex secretes DHEAS in an amount comparable to normal during physiological adrenarche. This leads to the development of pubic hair in both sexes to grade P III (darker, more curled, thicker hair, extending above the pubic symphysis). Menarche praecox can occur in girls with benign recurrent follicular ovarian cysts. [1,6]

2.5 Iatrogenic causes of precocious puberty

Most often this happens when children use cosmetics or medicines that belong to their parents and that contain exogenous androgens or estrogens. The product may be absorbed through the skin and, as a consequence, develop isosexual or heterosexual form of precocious puberty. The type of precocious puberty depends of the hormone used in the product and the child's sex. [1]

Treatment

Depending on the cause of precocious puberty, it may be appropriate to introduce surgical or pharmacological treatment. Indications for surgical treatment will be sex hormone secreting tumors, CNS tumors that give neurological or hormonal symptoms, as well as ovarian tumors and cysts. However, there are exceptions in which surgical treatment is replaced by chemotherapy and radiation therapy, which are germ cell tumors and optic glioma. Surgical removal of the lesions removes neurological symptoms, but not precocious puberty. Children should remain under strict control of sexual development, but also under oncological or neurosurgical control.

On the other hand, pharmacological treatment consists in inhibiting the secretion or action of GnRH and reducing the synthesis of peripheral sex hormones. For this purpose, it is used:

- long-acting GnRH (triptorelin) analogues in GnRH dependent precocious puberty
- hydrocortisone in congenital adrenal hyperplasia
- tamoxifen in McCune-Albright syndrome
- aromatase inhibitor in McCune-Albright syndrome (not simultaneously with tamoxifen!)
- androgen receptor inhibitor in testotoxicosis. [1,6,11]

Summary

Many factors are responsible for precocious puberty in children. The course of the disease affects both the physical and psychological sphere of the child. In order to compensate for the distant effects of this disease, it is necessary to detect symptoms early and implement effective treatment to avoid long-term complications. Emphasis should also be placed on health education to raise public awareness.

References:

1.Starzyk J. *Zaburzenia dojrzewania płciowego*. W: Kawalec W., Grenda R., Ziółkowska H. (red.) *Pediatria.* Warszawa: PZWL; 2013: 834-850.

2. *Przedwczesne dojrzewanie płciowe* W: Lissauer T., Clayden G. (red.) *Pediatria*. Wrocław: Elsevier Urban & Partner; 2013: 218-221.

3.Rzepka-Górska I. *Ginekologia dziecięca i dziewczęca* W: Bręborowicz G. (red.). *Położnictwo i ginekologia.* Warszawa: PZWL; 2014: 757-803.

4.Krysiak R, Marek B, Okopień B. *Przedwczesne dojrzewanie płciowe pochodzenia ośrodkowego.* Endokrynologia Polska. 2008 Oct 30;59(6):530-29.

5.Jarząbek-Bielecka G., Warchoł-Biedermann K., Sowińska E., Wachowiak-Ochmańska K. *Precocious Puberty*. Ginekologia polska. 2011;82(4).

6.Włodarczak A, Kurowska M. *Przedwczesne dojrzewanie płciowe u dziewcząt – diagnostyka i leczenie.* Klinika Pediatryczna. 2009, 17.

7.De Vries L, and Phillip M. *Role of pelvic ultrasound in girls with precocious puberty.* Hormone research in paediatrics. 75.2 (2011): 148-152.

8. Brito, Vinícius Nahime, et al. *Central precocious puberty: revisiting the diagnosis and therapeutic management*. Archives of endocrinology and metabolism 60.2 (2016): 163-172.

9. Ghaemi, N., Vakili, R. and Bagheri, S. (2013). *Precocious Puberty: An Unusual Presentation of Hypothyroidism.* International Journal of Pediatrics, *1*(2), 51-54.

10.Shozu, M., Fukami, M., & Ogata, T. (2014). *Understanding the pathological manifestations of aromatase excess syndrome: lessons for clinical diagnosis.* Expert review of endocrinology & metabolism, 9(4), 397-409.

11. Krysiak R, Marek B, Okopień B. *Peripheral precocious puberty.* Endokrynologia Polska. 2009;60(6):503-14.