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"PRECOCIOUS PUBERTY DEVELOPMENT. REVIEW OF LITERATURE"

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A B S T R A C T

In this article the authorscarried out a review of the literature on aspects of one of the current and little-studied problems in endocrinology, namely, the problems of premature sexual development. The article covers the issues of etiopathogenesis, classification, clinical picture, diagnosis and treatment of the disease.

The purpose of the study was to review the literature on precocious sexual development in children.
Material and research methods. Literature data for the last 10-15 years
Results. When faced with a PPD, you need to answer three questions.
1. Is PPD a normal variant or an abnormal sign?
2. If this is a deviation from the norm, is it central or peripheral, and if it is peripheral, then is it adrenal or gonadal?
3. If central, is it idiopathic or associated with intracranial pathology? Are there any indications for treatment?
If these questions are answered, then the diagnosis will be correct. Careful monitoring of all patients constitutes the main aspects of treatment.
Conclusions. Effective treatment with GnRH agonists can only be successful if Gn is effectively suppressed. Bone age, growth rate, uterine and ovarian size, and breast development should be closely monitored during treatment. The treatment does not affect pubic hair. LH suppression should be checked with an IV GnRH test at 3-6 month of treatment. Monitoring estrogen levels is not recommended.[16].

K E Y W O R D S

Precocious puberty, literature review. premature puberty, central, peripheral, adolescents.

Introduction

Definition of disease. The classic definition of precocious puberty is the development of secondary sexual characteristics before 8 years of age in girls and before 9 years of age in boys. It is classified as central precocious puberty, when there is premature maturation of the hypothalamic-pituitary-gonadal axis, and as peripheral precocious puberty, when there is excessive secretion of sex hormones, independent of the secretion of gonadotropins. PPD is more common in girls, usually central

precocious puberty of idiopathic origin. In boys, it is usually associated with abnormalities of the central nervous system.

The incidence of PPD ranges from 1/5000–1/10,000.[2,3]More common in girls. The female to male ratio ranges from 3/1 to 23/1.[4]It is reported to be more common in adopted children in developed countries.[5][16].

Pathogenesis. Central or true precocious puberty (iPPD) results from premature activation of the hypothalamic-pituitary-gonadal axis. It mimics physiological pubertal development, although it is at an inappropriate chronological age (up to 8 years in girls and 9 years in boys). This may be due to congenital brain malformations or acquired strokes, but in most cases the cause in girls remains unknown. MKRN3 gene defects have been identified in familial diseases, providing important baseline and clinical results. Indeed, genetic analysis of this gene should be included in routine clinical testing of familial and idiopathic cases of central precocious puberty, note the French authors. Gonadotropin-releasing hormone agonists are the gold standard of treatment. The evaluation and management of this disease remains a challenge for pediatric endocrinologists. In this series of articles, the authors described the current challenges associated with accurate diagnosis and adequate treatment of this disorder. [1].

Idiopathic central precocious puberty (ICPPD) or iPPD is a relatively common disorder among girls and its pathogenesis remains to be elucidated. A variety of studies have identified the association of gut microbiota (GM) with endocrine diseases such as obesity, which is commonly associated with ICPP. However, the relationship between CM and iPPD remains unexplored. Positive correlations were also found between Fusobacterium and follicle-stimulating hormone, and Gemmiger and luteinizing hormone. The implications of these findings remain to be determined [2].

The mechanisms of occurrence of true PPD have not been sufficiently studied to date. There is an assumption that certain lesions of the central nervous system, subcortical nuclei or hypothalamus affect centers that temporarily inhibit puberty, resulting in premature disinhibition of the hypothalamic-pituitary-gonadal system.

It is most likely assumed that these centers are located in the posterior hypothalamus, where organic brain lesions accompanying PPD are most often detected. The localization of cerebral damage leading to PPR affects the area behind the median eminence, mamillary bodies, the bottom of the third ventricle, and the epiphysis. Damage to other parts of the central nervous system (optic chiasm, infundibula, anterior hypothalamus) leads, as a rule, to delayed puberty (Zhukovsky M.A. et al., 1989).

Another short report aimed to examine the relationship between vitamin D and PPD. PPR patients and controls were selected for a systematic meta-analysis. The primary outcome was the mean difference in serum vitamin D levels. The results suggest that PPD may be associated with vitamin D deficiency. Thus, providing vitamin D supplements to patients with PPD can improve their nutritional status and prevent disease. But the amount of vitamin D needed is uncertain, so it is important to be careful when taking vitamin D [3].

iPPD results from early activation of the hypothalamic-pituitary-gonadal (HPG) axis and follows the same sequence as normal puberty. Although many factors influencing the onset of puberty remain poorly understood, the kisspeptin system is known to play a key role. Currently, mutations in the kisspeptin system, MKRN3 and DLK1 have been identified in sporadic and familial cases of CPP.

Diagnosis is based on physical examination findings indicating progression of puberty and laboratory studies demonstrating activation of the central HPA axis. [14].

Classification

iPPD is a common reason for referral to pediatric endocrinology clinics, where women predominate. PP is a broad term covering benign variants of normal development, gonadotropin-dependent pubertal development (GDP) and gonadotropin-independent precocious puberty (GIPD) [15].According to other authors, PPD can be classified as gonadotropin-dependent, progressive (central/true PPD), or gonadotropin-independent (peripheral/pseudo-PPD). The hypothalamic-pituitary-gonadal (HPG) axis is active both during physiological puberty and in the central true PPD. However, pseudo- or peripheral PPD is not dependent on gonadotropin secretion, and there is no activation of the HPG axis. The source of sex steroids in this subgroup is exogenous and/or endogenous.[16].

Clinical assessment should include a detailed history and physical examination, including anthropometric measurements, calculation of growth velocity, and assessment of secondary sexual characteristics. The main sign of the onset of puberty is the development of breast tissue (thelarche) in girls and testicular enlargement (≥4 ml) in boys. Hormonal assessment and imaging are essential for diagnosis and determination of etiology. Genetic testing should be considered if there is a family history of precocious puberty or other clinical features suggestive of a genetic syndrome. Long-acting gonadotropin-releasing hormone analogues are the standard of care for central precocious puberty, while peripheral management of precocious puberty depends on the etiology. premature puberty. The main sign of the onset of puberty is the development of breast tissue (thelarche) in girls and testicular enlargement (≥4 ml) in boys. The classic definition of precocious puberty is the development of secondary sexual characteristics before age 8 in girls and before age 9 in boys. • Long-acting gonadotropin-releasing hormone agonist (GnRHa) is the standard of care for chronic renal failure, and adequate hormonal suppression results in stabilization of pubertal progression, decreased growth velocity, and slower bone growth. • Most cases of precocious puberty are gonadotropin dependent and are currently considered idiopathic, but mutations have been identified in genes involved in pubertal development such as MKRN3 and DLK1.[4].

The authors retrospectively analyzed the clinical records of 55 children (36 girls) with precocious puberty. Most of them (34, 62%) had central precocious puberty, of which 19 were idiopathic. Peripheral precocious puberty was noted in 14 children. Congenital adrenal hyperplasia was the most common cause of peripheral precocious puberty (6, 42.8%).[5].

Diagnosis of PPD. Diagnosis of PPD should take place in 2 stages. The first stage is confirmation of the PPR. Clinical diagnosis is based on assessing the stage of sexual development according to the J. Tanner scale (Tables 1 and 2).

Anthropometry and calculation of the child's growth rate over the previous 6–12 months are mandatory. Exceeding growth rates (relative to the norm for a given age) and growth rates of more than 2 SD over the previous period indicate in favor of PPD. A necessary study to assess bone age is radiography of the hands and wrist joints. The advance of bone age in comparison with the passport age by more than 2 years confirms PPD.

Second stage— differential diagnosis of nosological forms of PPD in order to determine treatment tactics. This stage includes instrumental and laboratory research methods. During the diagnostic search, the results of the clinical examination are primarily taken into account. [10-13]:

The next step in the diagnostic search is the use of instrumental methods. Ultrasound examination of OMT allows not only to diagnose signs of PPD, but is also an additional method of differential diagnosis between true PPD and isolated thelarche.

Ultrasound signs of PPD are as follows [6]: an increase in the size of the uterus of more than 3.4 cm; formation of an angle between the cervix and the body; the appearance of the endometrium (M-echo) is a 100% sign, but the sensitivity of this criterion is low (42–87%); an increase in the size of the ovaries by more than 1–3 ml. The presence of single follicles does not allow differentiating PPD from isolated thelarche.

Detection of ovarian cysts helps in the diagnosis of gonadotropin-independent forms of PPD (McCune-Albright-Braitsev syndrome and follicular ovarian cysts).

Instrumental diagnostics for PPR may also include an MRI of the brain. MRI of the brain is performed when the gonadotropin-dependent nature of PPD is proven: in girls under 6 years of age it is mandatory; in girls with the onset of PPD between 6 and 8 years old, it is performed in the presence of neurological symptoms and signs of hypopituitarism.

Diagnosing PPR in a child with minimal symptoms can be difficult. The diagnosis of PPD, especially in girls, should be confirmed by increased levels of gonadotropins and/or sex steroids, accelerated somatic development and increased bone age. Monitoring for early signs of puberty is also important. If these signs do not progress during follow-up, early breast development can be considered normal.[16]:

Magnetic resonance imaging (MRI) of the skull and pituitary gland should be performed to rule out organic PPD. Although it has been suggested that MRI should be performed only in men or in girls younger than 6 years, it is now common practice to perform MRI in all cases because intracranial tumors can cause PPD at any age.[25824]However, imaging should be repeated periodically in cases where the child is younger than 4 years and considered normal. It is important that MRI images are evaluated by experienced radiologists. Flowcharts for PP for boys and girls are shown[16]:

Treatment of central PPD. Gonadotropin-releasing hormone analogues are currently used to treat true PPD. An indispensable condition for therapy with long-acting GnRH analogues is continuity of therapy, maintenance of a calendar and adherence to the injection regimen. Evaluation of the effectiveness of therapy is carried out no earlier than after 3 months. from the start of treatment, then every 6 months. based on a combination of clinical and laboratory indicators and includes: - examination of the child once every 6 months. (anthropometry, assessment of sexual development); - radiography of the hands once a year (with high rates of growth and progression of sexual development - once every 6 months); - instrumental studies (ultrasound examination of the pelvic organs - once every 6 months) ;— laboratory examination. Determination of the level of LH, FSH, estradiol - once every 6 months. (tests are carried out 1–3 days before the next injection of the drug), a test with GnRH is carried out after 6 months. from the start of therapy and with the progression of sexual development. A moderately elevated FSH level is not a sign of lack of effect of therapy.The pubertal growth suppression effects of growth hormone gonadotropin hormone agonists (GnRHa) during puberty are

well known, although it remains unclear whether long-term GnRH treatment affects brain function in treated children. The present study examined differences in homotopic resting functional connectivity patterns in girls with iPPD with and without GnRHa treatment using homotopic voxel mirror connectivity (HMC). Methods. Eighteen girls with iPPD who received 12 months of GnRHa treatment, 40 untreated girls with iPPD, and 19 age-matched girls with premature hair loss underwent resting-state functional magnetic resonance imaging. The GSVZ method was performed to study differences in interhemispheric resting-state functional connectivity. Levels of pubertal sex hormones including luteinizing hormone (LH), follicle-stimulating hormone and estradiol were assessed. Correlation analysis of the results of clinical laboratory tests, neuropsychological scales and GSVZ values for various brain regions was performed with data from the group receiving GnRHa. Results: Significant reductions in the SVG of the lingual, calcarine, superior temporal, and middle frontal gyri were found in the untreated group compared with the control group. In patients receiving treatment, a decrease in GSVZ in the superior temporal gyrus was found compared to controls. Compared with the non-medicated group, the drug-treated group showed a significant increase in SVG in the calcarine and middle occipital gyrus. In addition, a positive correlation was observed between basal LH levels and the VMHC of the middle occipital gyrus in medicated patients. These data indicate that long-term GnRH treatment was associated with increased functional interhemispheric connectivity in several regions involved in memory and visual processing in patients with STIs. Higher interhemispheric functional connectivity in the middle occipital gyrus was associated with higher basal LH output in treated girls. This study adds to the growing body of research into the effects of GnRHa on brain function.[8]:

During GnRH, the ovarian reserve of the SRR is somehow suppressed by the treatment, but is gradually restored after the drug is discontinued. Thus, GnRHa treatment does not affect the ovarian reserve in children after treatment stops [9]:

GnRH analogues are the mainstay of treatment and are used to preserve growth. Development of new extended-release formulations continues. There are currently no data on long-term complications associated with treatment. However, many areas remain to be explored, such as targeted therapy and clinical management aspects. Further research into the psychological effects and more data on long-term outcomes are needed, especially in men. [14].

Thus, When faced with a PPD, you need to answer three questions.

1. Is PPD a normal variant or an abnormal sign?
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If these questions are answered, then the diagnosis will be correct. Careful monitoring of all patients constitutes the main aspects of treatment.

Conclusions

Effective treatment with GnRH agonists can only be successful if Gn is effectively suppressed. Bone age, growth rate, uterine and ovarian size, and breast development should be closely monitored during

treatment. The treatment does not affect pubic hair. LH suppression should be checked with an IV GnRH test at 3-6 month of treatment. Monitoring estrogen levels is not recommended.[16].

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