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EARLY PUBERTY: A LITERATURE REVIEW

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Abstract: Precocious puberty can be defined as the development of secondary sexual characteristics before the age of 8 in girls and before the age of 9 in boys, which can be caused by hormonal disorders, genetic changes or exposure to chemical substances. The objective of the work was to analyze the main etiologies, diagnosis, epidemiology and clinical evolution and treatment of precocious puberty, aiming to improve the clinical understanding of the pathology. This is a bibliographic review type research, which included articles in Portuguese and English published between 2014 and 2024 in the UpToDate, SciELO and BVS databases. Articles out of date, not available online or repeated were excluded. The review carried out reveals that there are several etiologies for precocious puberty, which are classified into central causes (early activation of the hormonal axis itself) or peripheral causes (external autonomous production of sexual steroids). Depending on the type of etiology, the diagnostic method is chosen, which consists of clinical factors, hormonal levels and imaging, such as wrist radiography to assess bone age. Furthermore, the clinical evolution of the disease progresses with initial presentations such as breast development in girls and increased testicular volume in boys, increased growth speed and skeletal maturation, in addition to the emergence of other sexual characteristics. Regarding treatment, the aim is to suppress the production of gonadotropins (LH and FSH) through the use of long-acting GnRH agonists, in patients with clinical indication.
Keywords: precocious puberty, secondary characters, central precocious puberty, peripheral precocious puberty.

INTRODUCTION

Puberty is the process of biological maturation that encompasses the transition period between childhood and adulthood. It is marked by hormonal changes, which culminate in the appearance of secondary sexual characteristics, the acceleration of growth rate and gonadal maturation, in addition to the acquisition of reproductive capacity and psychological changes. It is the result of increased secretion of gonadotropin-releasing hormone (GnRH), which stimulates the secretion of luteinizing (LH) and follicle-stimulating hormones (FSH), which in turn will stimulate the secretion of sex steroids and promote gametogenesis[1].

Therefore, it is considered precocious when secondary sexual characteristics appear before the age of 8 in females and before the age of 9 in males. In 80% of cases, sexual precocity is dependent on gonadotropins, also called central precocious puberty (CPP) or true puberty, which results from premature activation of the gonadotropic axis. The initial manifestation in girls is the appearance of the breast bud and in boys an increase in testicular volume greater than or equal to 4 mL. For both sexes, there may be early fusion of the bone epiphyses, which anticipates the end of growth and may compromise final height. It is seen as a rare condition, being 10 to 23 times more common in girls than in boys.

In a smaller number of cases, with no epidemiological data on incidence and prevalence, it is classified as peripheral precocious puberty (PPP) - also known as precocious pseudopuberty or gonadotropin-independent precocious puberty -, resulting from autonomous production of sexual steroids, or that is, a consequence of ovarian tumors or cysts, testicular tumors, congenital adrenal hyperplasia, adrenal tumors, McCune Albright Syndrome, severe hypothyroidism, among other diseases.

The diagnosis is based on a detailed clinical history, which is capable of inferring extremely relevant data for investigating the etiology, accompanied by physical examination, laboratory tests and imaging. Treatment varies depending on the etiology, with pubertal blockade using GnRH agonists being one of the most used methods for PPP and for the management of PPP, it is necessary to treat the underlying cause.

METHODOLOGY

This is a literature review, developed based on articles published between 2014 and 2024 in the electronic databases: UpToDate, Scientific Electronic Library Online - SciELO and Biblioteca Virtual em Saúde - VHL, using the descriptors: precocious puberty, precocious puberty central, peripheral precocious puberty, puberty and their respective synonyms, in Portuguese and English. Only published articles that dealt with the topic and were available online were included. Articles outside the proposed period, which did not deal with the topic, were not available online and repeated articles found in different databases were excluded.

REVIEW OF LITERATURE

Precocious puberty is traditionally defined as the onset of secondary sexual characteristics before the age of eight in women and nine years in men, puberty <8 years in girls, and <9 years in boys. This phenomenon can be caused by a variety of factors, including hormonal disorders, genetic changes and exposure to chemicals that interfere with the endocrine system[4]. Approximately half of the patients had central precocious puberty (CPP). Distinct genetic causes were identified in 12.6% of patients with apparently idiopathic CPP, which shows a relevant genetic impact for both sexes. Despite this, the prevalence in females is still higher[4].

Family history and neurodevelopmental disorders have been suggested as predictors of genetic CPP. Originally, an algorithm was proposed to investigate the etiology of CPP, including genetic studies, which are still ongoing[3].

Another study from the United States demonstrated a median age of breast development of 8.8 years in black girls, 9.3 years in Hispanic girls, and 9.7 years in Asian and non-Hispanic white girls. Body mass index accounted for a greater proportion of this variation (14 percent) compared to race/ethnicity (4 percent). Although some guidance has suggested that race/ethnicity must be incorporated into decisions about thresholds for precocious puberty assessment, the validity and basis of this approach must be critically considered. Associations between genetic ancestry and the timing of puberty have been reported, but the correlation is relatively weak, is not observed in all population groups, and decreases with population diversification. Furthermore, race/ethnic groups represent social constructs that are often poor proxies for genetic ancestry. For these reasons, it remains unclear to what degree race/ethnicity is an independent modifier as opposed to a marker for other factors that affect pubertal timing, such as body mass index, exposure to chemicals that disrupt endocrine metabolism, and/or other social determinants of health. It is important to incorporate all available clinical information when deciding whether to evaluate a child with precocious puberty, such as family history, body mass index, or researching idiopathic causes, such as the use of chemicals that modify metabolism.

The diagnosis of precocious puberty initially involves differentiating central precocious puberty from peripheral precocious puberty. The first normally imitates physiological puberty but at an early age, while the peripheral one has a disordered appearance of the pubertal phases with a rapid progression.

> Both to differentiate the types of precocious puberty and to exclude other diagnoses, the following must be carried out: clinical assessment of the patient, hormonal assessment and imaging tests. (VILAR, 2020).

In clinical evaluation, several data may be relevant for an accurate diagnosis of precocious puberty, such as: age at which secondary sexual characteristics appear and their evolution since then, whether the patient has already taken or is currently using medications that contain steroids, history of trauma, CNS infections and chronic diseases, what were the conditions of pregnancy and childbirth and whether there is a family history of precocious puberty.

> However, during the physical examination, it is necessary to measure the patient's BMI, analyze height and weight according to chronological age and describe secondary sexual characteristics, in addition to classifying them according to the Marshall and Tanner stages (VILAR, 2020).

After clinical evaluation and a concrete suspicion of precocious puberty, it is necessary to carry out a hormonal assessment of the patient. Thus, the main test is measuring gonadotropins at baseline and after stimulation with GnRH, the cutoff value varies depending on the laboratory method used. FSH values are not useful unless they are suppressed, thus indicating peripheral precocious puberty. In boys, the testosterone value is useful for diagnosis, whereas in girl's pre-pubertal estradiol concentrations do not affect the diagnosis.

> Measurements of hCG, TSH, free T4 and adrenal androgen precursors are important for differential diagnosis (VILAR, 2020).

Another important step for diagnosis is imaging exams, X-rays of the wrist and non-dominant hand to assess bone age are necessary in both sexes.

> This is the main predictor of central precocious puberty when GnRH stimulation test is positive (XU, 2018).

In girls, abdominal US is recommended mainly to evaluate the uterus and ovaries.

> If there is a confirmed diagnosis of central precocious puberty, CNS evaluation is performed, normally through MRI, and is always recommended in girls under 6 years of age and in boys under 8 years of age, beyond this there is no defined benefit due to the large number of cases. idiopathic in this range (VILAR, 2020).

Clinically, precocious puberty is characterized by the emergence of sexual characteristics before the age of 8 in girls and before the age of 9 in boys, in association with accelerated linear growth and advancement in bone age[6].

It may occur due to premature activation of the hypothalamic-pituitary-gonadal (PPC) axis or, more rarely, as a result of the secretion of sex steroids, independently of the activation of the gonadotropic axis (peripheral precocious puberty, PPP). In PPC, secondary sexual characteristics are consistent with the patient's sex (isosexual). Meanwhile, peripheral precocious puberty can lead to an isosexual or heterosexual pattern, which is characterized by the discordance between pubertal characteristics and the patient's sex[5].

Central precocious puberty, when mimicking physiological puberty, generally has the same order of appearance of sexual characteristics, defined as thelarche, pubarche and, later, menarche. The interval for the evolution of a pubertal stage is, on average, 6 months. Differently, peripheral forms of precocious puberty can be characterized by rapid evolution and disordered appearance of pubertal signs. [6], menarche may be the first manifestation[5].

The initial presentation is characterized by breast development in females and an increase in testicular volume ≥ 4 mℓ or testicular length > 2.5 cm in males, assessed using the Tanner and Marshall criteria[6]. In peripheral presentation, testicular volume is generally reduced, except in cases of testotoxicosis, testosterone-secreting testicular tumors, presence of adrenal remnants and hCG-producing tumors. The premature appearance of pubic hair is also a manifestation of precocious puberty[5].

Both forms are characterized by accelerated growth rate and skeletal maturation, resulting in premature fusion of the bone epiphyses and compromising final height. In boys there is the appearance of facial hair and penis enlargement. Furthermore, some physical signs such as the appearance of acne, excessive oiliness of the skin and hair, axillary hair, body odor and muscle development are generally present in precocious puberty[6].

Treatment for CCP aims to temporarily suppress the production of gonadotropins, thereby controlling the production of sex hormones, and treating the underlying cause when identifiable. The therapy of choice is long-acting GnRH agonist analogs (a-GnRH), developed to suppress the activity of the gonadotropic axis. These compounds, such as leuprolide acetate and triptorelin, act competitively on GnRH receptors in the pituitary gland, leading to the down-regulation and reduction of receptors, and consequently the suppression of LH and FSH secretion[5].

Treatment of puberty includes detecting and arresting sexual maturation until the normal age for pubertal development, promoting stabilization of secondary sexual characteristics, delaying bone maturation, reducing the risk of sexual abuse and early initiation of sexual activity, and reducing the risk of body disproportions[2].

The indications for starting treatment with pubertal block are based on anthropometric and psychological parameters, including accelerated pubertal development, inadequate

final height potential, psychosocial changes such as behavioral disorders, emotional immaturity and mental retardation[6].

Monitoring of CPP treatment with GnRH analogues is based on quarterly clinical assessment, consisting of a physical examination and verification of pubertal staging, anthropometric assessment and calculation of growth speed. The objective of treatment is to reduce the levels of gonadotropins and sexual steroids (testosterone < 12 pg/dℓ for boys and estradiol < 15 pg/mℓ for girls) [6].

Suspension of treatment must be based on several criteria, such as the patient's chronological age and psychosocial adequacy. A bone age of around 12.5 years in girls and 13.5 in boys indicates the best time to suspend with the aim of achieving a normal final height, within genetic potential [6].

FINAL CONSIDERATIONS

Precocious puberty, defined as before age 8 in girls and before age 9 in girls, can be caused by numerous factors, including hormonal disorders, genetic changes, and exposure to chemicals. Diagnosis begins by differentiating central precocious puberty from peripheral precocious puberty.

The first normally imitates physiological puberty but at an early age, while the peripheral one has a disordered appearance of the pubertal phases with a rapid progression. Approximately half of the cases are of central precocious puberty, mostly female patients. Treatment occurs according to the etiology, and clinical evolution permeates the age of diagnosis, treatment and adherence.

In this sense, scientific studies on the subject are extremely important, as it can compromise health and well-being as adults, as well as short stature and psychosocial disorders if adequate diagnosis and treatment do not occur.

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