Review

Pathophysiology of Peripheral Precocious Puberty in girls: an overview

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ABSTRACT

Precocious puberty can be distinguished in central, or peripheral, based on the presence or absence of the Hypothalamic- Pituitary- Gonadal axis activation. The pathogenesis of peripheral precocious puberty (PPP) is based mainly on excessive estrogenic exposure, either endogenous or exogenous. The congenital causes of PPP include McCune- Albright syndrome (MAS) and Congenital Adrenal Hyperplasia (CAH). The main causes of acquired PPP are oestrogen producing tumours, which are mainly of ovarian or adrenal origin, hypothyroidism and environmental oestrogens or substances with estrogenic function.

Key Words: *precocious puberty, peripheral, pseudopuberty, pathogenesis*

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Introduction

Puberty is considered as a crucial developmental period, characterized by many physical, psychological, and social changes. It is known as a time of growth acceleration, gonad maturation (morphological and functional), as well as a period of increased sex steroid gonadal hormone secretion (testosterone for males, oestradiol and progesterone for females) and, finally, of gain of reproductive capacity (1). Steroid sex hormones are responsible for the development of secondary sexual characteristics, including the breast development and menstruation due to uterine maturation, in girls.

Physiology of Pubertal Onset

Physiologically, pubertal changes are incited by the reactivation of the Hypothalamic- Pituitary- Gonadal (HPG) Axis, because of an increase in Gonadotropin Releasing Hormone (GnRH) pulsatile secretion, resulting in Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) secretion (1,2). Naturally, this birth-active neuroendocrine axis, is suppressed during childhood, only to be reactivated at the beginning of puberty.

The exact mechanism that causes GnRH pulses to increase in amplitude is not yet elucidated. However, peptides, such as kisseptin, neurokinin-B and dynorphin have been proven to play a major role in GnRH secretion (1). Leptin, a hormone produced by adipocytes, that mainly acts as an appetite suppressor, by inhibiting neuropeptide Y (NPY), also seems to upregulate GnRH secretion. The timing of pubertal onset is defined by hormonal, genetic as well as environmental factors, including obesity, nutrition, general health and exercise (1,2).

In girls, breast development, termed as thelarche, is considered as the landmark of entrance to the pubertal age, since it is controlled by oestrogens (2). Menarche, usually, follows after approximately two years (3).

The aim of this review was to collect available data, regarding the pathophysiologic mechanisms involved in peripheral precocious puberty and enlighten some dimensions of this topic that remain unanswered.

Definition

Precocious puberty is defined as development of secondary characteristics of sex, occurring at an ageof 2.5 SD before the mean age in girls of the same population.

In most Western countries, this translates as onset of puberty before the age of 8 years old in females, and 9 years old in males. Menarche before 10 years of age is also defined as precocious puberty by some. Precocious puberty can be distinguished into two separate subtypes: central and peripheral. In central precocious puberty (CPP), there is premature activation of the HPG axis, resulting to sex steroid hormones production. Conversely, in peripheral precocious puberty the hypothalamus and pituitary gland remain suppressed, while there is sex steroid overproduction-for- age in the periphery. Sites of production include the gonads, the adrenals, and ectopic secretion, while exogenous oestrogen exposure may also trigger early pubarche (2,3).

Peripheral Precocious puberty

"Pseudopuberty" is a term commonly used for Peripheral Precocious Puberty (PPP), since the increase in GnRH pulses, which constitutes the normal inciting event for pubarche, is absent. On the contrary, the elevated concentration of estrogens in the periphery creates negative feedback, suppressing the hypothalamus and pituitary gland. Thus, minor reaction is noted during LHRH stimulation testing (3,4).

The main causes of precocious puberty in girls are distinguished into two categories (genetic and acquired) and summarised in Table 1 (1).

McCune- Albright Syndrome (MAS)

MAS is a rare disorder, of an estimated prevalence between 1/100.000 and 1/1.000.000, defined by the triad of polyostotic fibrous dysplasia, café- au- lait skin spots and precocious puberty (5,6). Among the many endocrinopathies arising in the setting of MAS, autonomous ovarian activation seems to affect a percentage of 85% of patients (7).

The genetic base of MAS is relatively complex. The syndrome has been attributed to postzygotic mutations in the GNAS gene locus. The most common mutation results in the substitution of arginine by histidine in the position 201 of the Gsa protein. Different mutations have also been found but are less common. (8) The GNAS gene encodes the Gsa subunit of a G signalling complex, that resides in many tissues involved in MAS. Consequently, the mutations described above lead to the production of a Gsa subunit that is constantly activated and, there-

-fore, to a substantial increase in intracellular cAMP, which, in turn, enhances the production and secretion of hormones in affected tissues. Patients with MAS represent somatic mosaics, as suggested by the fact that disorders commonly affect only one side of the body, "respecting the midline". This theory also explains the wide variety in clinical presentation (5,6,9).

Interestingly, there have been reports of progression from PPP to CPP in girls of advanced bone age (over 11 years old). PPP in girls with MAS can occur from neonatal years to early childhood and is induced by hyperactivated follicular ovarian cells, forming unilateral cysts, independently of gonadotropin stimulation. These cysts are morphologically complex, consisting of liquid, solid as well as haemorrhagic components and are responsible for the secretion of high levels of estrogens. Consequently, girls typically present with vaginal bleeding, which might or might not be accompanied by breast development and body growth. Vaginal bleeding might be episodic or recurrent, with irregular intervals, possibly persisting until adulthood (9, 10).

Congenital Adrenal Hyperplasia

Congenital Adrenal Hyperplasia (CAH) is a term describing a group of autosomal recessive diseases, caused by defects in enzymes of the adrenal cortex. These enzymes participate in the biosynthetic pathway of adrenal steroids. In 95% of cases, CAH results from mutations that decrease activity of 21-hydroxylase, an enzyme responsible for cortisol and aldosterone production. Decreased production of these two hormones stimulates adrenocorticotropic hormone (ACTH) secretion by the pituitary gland. Androgenic production is independent of 21-hydroxylase activity. Thus, ACTH stimulates androstenedione and DHEA production by the adrenal cortex, which are then converted to testosterone. An 11 beta hydroxylase (11OHase) deficiency, 3 beta hydroxysteroid dehydrogenase(3βHSD)deficiency, p450oxidoreductase deficiency, 17 hydroxylase deficiency and lipoid CAH (StAR) deficiency are reported as less common causes of CAH (10,11).

CAH due to 21-hydroxylase deficiency has an average prevalence of 1/15.000 births, even though countries that implement neonatal screening, such as as Sweden, report a higher incidence and better prognosis. CAH is distinguished in two forms, classic and non- classic. Classic CAH is, in turn, subdivided into a salt-wasting and non-salt-wasting form, based on 21-hydroxylase activity. In the former, 21-hydroxylase activity is excessively low, resulting in aldosterone insufficiency and sodium wasting through urine. Virilisation is severe, with ambiguous external genitalia, ranging from clitoromegaly to a common urogenital tract. In the latter, serum sodium is preserved due to adequate levels of aldosterone. In this case, virilisation occurs, but is usually less severe. In both forms internal genitalia remain unaffected. The non- classic form of adrenal hyperplasia (also known as "late onset CAH") typically presents later in life with a milder clinical appearance, characterized by oligomenorrhea, hirsutism and/or infertility (10,11).

Androgen excess results in early growth spurt, with advanced skeletal maturation, but eventual degradation of height potential. Consequently, the average adult height of CAH patients is significantly lower than that of the average population. Adolescent and adult women with CAH might suffer from hirsutism and other androgen-mediated gynaecologic disorders, including menstrual irregularities and infertility.

Ovarian tumours and cysts

Ovarian tumours are responsible for precocious puberty in 11% of affected girls. Some of these tumours secrete estrogens, able to cause breast development and vaginal bleeding (12).

Ovarian sex- stromal tumours consist of granulosa cells, sertoli cells, theca cells, leydig cells, and fibroblasts of gonadal stromal origin. Among them, juvenile granulosa cell tumours (JGCT) represent 67% of sex-stromal tumours during childhood. JGCT produce sex steroids and are, therefore, responsible for precocious puberty or virilization, when they occur in adolescence or later in life (13). Malignant germ-cell tumours account for 2.9% of all malignant childhood tumours, in patients younger than 15 years old. Tissues that are affected, other than the ovaries include the CNS, the coccyx, the testes, retroperitoneum, and mediastinum (15, 16). These tumours, especially of ovarian origin, can produce β-

Table 1. Causes of PPP in girls can be distinguished into genetic or acquired.

Causes of PPP in girls	
Genetic	**Acquired**
McCune- Albright Syndrome (MAS)	Ovarian Tumours
Congenital Adrenal Hyperplasia (CAH)	Ovarian Cysts
	Adrenal Gland Tumours excreting sex steroids Hypothyroidism
	Exogenous estrogenic exposure

Table 2. EDRs and their actions in girls (25,26,27)

EDR	Use	Action in girls	Mode of Action
DDT	Pesticides, Antimalarial	Early menarche, increase in danger of breast cancer	Binding to ERs
Dioxin	Industrial process	Breast development in prepubertal girls	Estrogenic, anti-estrogenic, alterations in gene expression [25,26]
Bisphenol A (BPA)	Polycarbonate plastics, epoxy resins	Precocious puberty, Dibetes, Heart disease	Binding to ERs, promotion of immature glycuronidation activity
Polybrominated biphenyls (PBB)	Plastic protection from burning	Early menarche, thelarche, pubic hair development	Estrogen antagonists(?)
Phthalates	Plastic food containers	Defeminization, Breast development	ERα and ERβ binding
Atrazine	Herbicide	Increase in danger of breast cancer	Increase in aromatase
Zeranol	Meat and grains	Breast development	Interference in the cell cycle, binding to ERs
Isoflavones	Food	Breast development, Breast cancer, Precocious puberty	

HCG, imitating the actions of LH and only partiallythose of FSH. Thus, ovarian theca cells are stimulated to produce androgens. Still, FSH is needed to enhance aromatase activity, so that androgens are converted to estrogens. This process takes place in granulosa cells. That is why, some suggest that, in girls with germ-cell tumours, aromatase activity depends on different factors (16).

Adrenal tumours

In girls, PPP due to adrenal tumours is extremely rare. Adrenocortical tumours represent less than 0.2% of pediatric tumours. Girls present a two-fold increase in risk of presenting an adrenal tumour, compared to boys. The most common presenting signs and symptoms result from virilization (17). Feminizing tumours are even more rare. From 1922 to 1982, there were reports of only 10 cases of girls with precocious puberty, caused by feminizing adrenal tumours (18). Often, adrenal tumours of childhood arise as a manifestation of genetic syndromes, such as Li- Fraumeni or Beckwith–Wiedemann syndrome.

Hypothyroidism

Juvenile hypothyroidism is a rare cause of precocious puberty. PPP typically arises in the setting of severe hypothyroidism and can manifest as breast tissue enlargement, maturation of the external genitalia and even vaginal bleeding. Growth retardation is another common finding. Interestingly, pubic hair, which is a feature of androgenic function, is absent in precocious puberty of juvenile hypothyroidism (19). Another notable element is the fact that symptoms are completely reversible once thyroid hormone is replaced.

The exact pathophysiologic mechanism of precocious puberty in hypothyroidism is still under investigation. Many hypotheses have been proposed over the years. In 1960, Van Wyk et al. suggested that precocious puberty and juvenile hypothyroidism could result from ‘nonspecific overproduction of multiple pituitary hormones’, incited by thyroid failure (20). Another theory focuses on estrogen metabolism disorder, caused by decreased thyroxine. However, the exact metabolic effects of hypothyroidism in estrogens remain unknown (19).

According to Hemady Z. S. et al, the predominant theory is that precocious puberty in juvenile hypothyroidism is a result of increased levels ofprolactin. TSH overproduction, seen in primary hypothyroidism is often accompanied by prolactin elevation, due to TRH stimulation. This theory suggests that prolactin has an immediate effect on ovarian cells, resulting in estrogen secretion (19).Koutras, on the other hand, refers to a «spillover» effect of TSH, which can have effects similar to LH and FSH, leading to early or -more commonly- delayed pubarche (21).

Environmental estrogens

Fetal and childhood exposure to estrogens is considered as a possible cause of many adverse events in later life, including precocious puberty. Even low doses of steroids can exert severe disruption of the fine balance between pituitary gland and the gonads (23). On the contrary, Partsch et al. estimated that estrogenic contamination of food could not constitute a valid cause of precocious puberty, since it is not systematic, but rather sporadic (5).

Endocrine disruptors (EDRs) are natural or artificial chemicals, that have an impact on the human endocrine system (23). The establishment of a causative relation between endocrine disruptors and sexual precocity is hard, mainly, because of the wide range of chemicals present in the environment, in combination with the long latency period between perinatal exposure and puberty. EDRs are substances, present in many widely used objects, including drugs, pesticides, detergents, fertilizers and heavy metals (24). Because of their similarity to natural hormones, EDRs can act as estrogenic or androgenic agonists or anti-agonists, or have effects on GnRH, leading to peripheral or central precocious puberty. As far as the estrogenic effects are concerned, they might be exerted via immediate action on estrogenic receptors of oestrogen- sensitive tissues, aromatase action enhancement, or augmentation of tissue sensitivity to estrogens (24,25). The main EDRs, connected to precocious puberty in girls are shown in Table 2.There is disagreement among different studies on the exact role and effect of some substances, accused as EDRs. For example, while BPA is commonly accused of causing precocious puberty in girls, Yum et al. (26) failed to track high levels of these substances in the blood of girls with precocious puberty. On the

contrary, levels of BPA and phthalates were higher in the blood of healthy controls.

Prevention of precocious puberty and other endocrine abnormalities could be achieved by controlling the exposure to EDRs. Many countries have already prohibited the use of some substances with proven effects on endocrine tissues. However, more research needs to be conducted, in order to clarify the exact impact and mechanism of action of certain substances in estrogen- dependent tissues and overall health.

Conclusion

The pathogenesis of peripheral precocious puberty, also termed pseudopuberty, is quite variable, since it can be attributed to many different causes, genetic or acquired. What is common in every case of peripheral precocious puberty is the excessive estrogenic secretion, which is independent of the hypothalamic-pituitary regulation.

Early detection of signs of pubertal precocity, such as thelarche, menarche or pubarche is crucial and should prompt immediate referral to a paediatric gynecologist or endocrinologist for further investigation. Specialist intervention can be of vital importance and even completely reverse pubertal onset, as can happen in precocious puberty, in the setting of severe hypothyroidism.

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