


Case Report of Central Precocious Puberty in a Female: Role of Environmental Pollutants?

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ABSTRACT: A 5-year-old girl was brought to Department of Pediatric Endocrinology and Diabetes for premature breast development since 4 months. Her medical antecedents and family history were uneventful. From investigations she was diagnosed as a case of central precocious puberty. Identification of pesticides in farms surrounding their house indicates that this early stimulation of the hypothalamic-pituitary-gonadal axis was linked to the estrogen-like activity of endocrine-disrupting compounds.

KEYWORDS: Endocrine disrupters, pesticides, precocious puberty

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Introduction

Puberty is multifaceted developmental phenomena that begins in late childhood and is characterized by maturation of the hypothalamic-pituitary-gonadal axis. In addition to the appearance of secondary sexual characteristics, there is acceleration of growth as well as the start up of fertility.^{1,2}

Precocious puberty (PP) is defined as the onset of developmental signs of sexual maturation earlier than population's norms, typically before 8 years in girls and 9 years in boys.³

While genetic factors is the main determinant of pubertal timing, the tendency into an earlier age of puberty in the last century coincided with improvements in lifestyle, and recently these changes have been assigned to obesity. It has also been wondered that endocrine-disrupting compounds (EDCs) are potential contributors to this abnormal process.^{4,5}

We report an uncommon case of PP in a 5-years-old girl. Endocrine analysis showed a central origin responsible for early pubertal timing. This case report highlights the effects of pesticides on pubertal timing.

Case Report

A 5-year-old girl presents to our pediatric endocrine unit for breast enlargement since 4 months. She had no history of headache, visual problems, behavioral changes, or neurological deficits. There was no history of head trauma or surgery, no gelastic seizures, history of encephalitis, or radiation exposure. Family history was unremarkable and perinatal period was uneventful. Physical examination displayed a girl with weight = 21 kg ([medium] M), height = 128 cm (+2 [standard derivation] DS), mid-parental height is 157 cm (-). She had a normal psychomotor development. The patient presented an elevated Areola above contour of the breast, forming “double

scoop” appearance (Tanner stage 4); there was Downy pubic hair (Tanner stage 1) and no axillary hair. Abdominal examination did not revealed any masses. Hand Bone Age according to Greulich and Pyle atlas is advanced over chronological age by ~3 years. Pelvic ultrasound revealed an uterine long axis of 55 mm (normal 35 mm), anteroposterior diameter of 9.7 mm, transverse diameter of 6.6 mm, and a large a central vacuity line. A uterine body/cervix ratio > 1, there were 3 increased follicles in the ovary, and the maximum diameter of follicle was 9 mm without ovarian cysts or pelvic mass.

Endocrine analysis, presented in Table 1, showed high estrogen value: 18.29 pg/mL.

A Decapeptyl is agonist of gonadotropin releasing hormone (GnRH) available in morocco.

The Decapeptyl test was performed at 8:00-8:30 a.m. An intravenous (IV) cannula was inserted and blood samples were collected for basal follicle-stimulating hormone (FSH) and luteinizing hormone (LH). Following administration of a standard dose of 100 mg decapeptyl, blood samples for FSH and LH were obtained at the 15th, 30th, 45th, and 60th minutes. FSH and LH were measured using chemiluminescent microparticle immunoassay.

Decapeptyl test showed a predominant FSH response (FSH increased from 3.8 mUI/mL to 5 mUI/mL), while the LH presented a modest response (LH increased from 0.9 mUI/mL to 7 mUI/mL), LH/FSH > 1. These facts are suggesting a central precocious puberty (CPP). For this reason, we realize cerebral magnetic resonance imaging to exclude a central nervous system injury.

There was no antecedent of excessive soy or estrogen intake. The patient lived on a farm where several pesticides were stocked. To demonstrate that this CPP was associated with



Table 1. Decapeptyl test.

	T0	T15	T30	T45	T60
FSH (mIU/mL)	3.8	4	5	5.6	5
LH (mIU/mL)	0.9	5	7	8	10
Estrogène (pg/mL)	18.29				

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.

pesticides contamination, we obliged the family to move away from pesticides. After 1 year, the patient had a normal hormonal balance, stabilization of ultrasound measurements of the uterus and ovary, and stabilization of height.

Discussion

Puberty is having many facets that may be monitored by different parameters. External symptoms such as the development of breasts in girls, the increase in testicular volume in boys, and pubic hair growth are staged in adolescents according to criteria defined by Marshall and Tanner.^{7,8}

PP is a spreading problem especially in girls and may lead to psychological problems due to early maturity and short stature due to early closure of the epiphyses. On the other hand, prolonged exposure to estrogens can increase a risk of breast cancer in adulthood.⁹ Then, early diagnosis and treatment is required.

PP is diagnosed by determining early secondary sexual characteristics, accelerated body growth, and advanced bone age, as well as increased levels of gonadotropins and/or sex steroids. Cases in which breast development is observed without advanced bone age or accelerated body growth are referred to as isolated early thelarche.^{10,11} Premature thelarche is usually slowly progressing or even spontaneously limited but can occasionally convert into central precocious puberty.¹²

PP can be categorized as either gonadotropin-dependent (central/true) or gonadotropin-independent (peripheral/pseudopuberty). The differentiation between gonadotropin-dependent and gonadotropin-independent precocious puberty is an important step in the proper diagnosis and prompt treatment of patients with precocious puberty (Table 2).^{13,14} In gonadotropin-dependent PP, the hypothalamic-pituitary-gonadal (HPG) axis is activated, as also noticed in physiological puberty. On the other side, in gonadotropin-independent puberty, the HPG axis is suppressed, and PP is not dependent on gonadotropin secretion. This group of PP is dependent on endogenous and/or exogenous sex steroids.^{10,11}

Gonadotropin-dependent precocious puberty, also referred to as central precocious puberty, is characterized by premature activation of the GnRH pulse generator.¹⁵

The diagnostic of central PP⁹:

1. A difference of > 1 between bone age and chronological age;
2. The basal LH > 0.6 mIU/mL;

3. Basal estrogen > 12 pg/mL;
4. LH > 5 mIU/mL after GnRH stimulation;
5. LH / follicle-stimulating hormone > 1
6. Thickness of the uterine endometrium > 2 mm and/or the length of the uterus > 3.4 cm; and
7. Ovarian volume > 1 cm³

Recent studies have noted a general tendency toward earlier puberty development. It is believed that this early onset is multifactorial: environmental, hormonal, and genetic.

Endocrinal disruptors (EDs) are environmental compounds, which may be either natural or synthetic. EDs accumulate in the environment in the long term and are introduced into the human body through water, foodstuffs, and air or via furniture of the office and home. Furthermore, it has been proved that these chemical compounds can pass on to fetus by placenta or to baby by breastfeeding.⁶

Theoretically, substances with hormone-disrupting capability may affect pubertal development by acting at several levels: the hypothalamic-pituitary axis, the gonads, and peripheral target organs such as breasts, hair follicles, and genitals.¹⁶

In the brain, endocrinal disruptors can stimulate the estrogen-sensitive nuclei, hypothalamic neurons, through releasing kisspeptin and boosting the maturation of the hypothalamus causing earlier onset of puberty, or even PP. However, other compounds could act by gonadotropin inhibition through negative feedback. It is also possible that EDs have direct effects on both the body weight and the endocrine system of the HPG axis.¹⁶

Steroids from the adrenal glands also contribute to normal progression of puberty, such as pubic hair development. A disorder of the adrenal gland generated by EDs can affect the estrogenic hormonal conditions and consequently also perturb pubertal development.¹⁷

The effects of pesticides on the endocrine system are agonistic or antagonistic due to their hormone-like characteristics. Their effects on puberty are estrogenic, antiestrogenic, androgenic, and antiandrogenic and directly on the GnRH system.¹⁸

These endocrine-disrupting compounds apply their estrogenic effects by directly binding to estrogen receptors, boosting aromatase activity and sensitivity to estrogen or raising endogenous estrogen production through the GnRH system, which can ultimately cause PP. The antiestrogenic and androgenic actions of these chemicals are often expressed by inhibiting an aromatase enzyme activity and the steroidogenic enzyme production system. They exert their antiandrogenic effects by suppressing testicular steroidogenesis and blocking androgen receptors.¹⁸

Researchers found puberty timing associations with these chemicals¹⁹:

- Triclosan, used as an antibacterial agent in some toothpaste and hand soap

Table 2. Differences between gonadotropin-releasing hormone (GnRH)-dependent and GnRH-independent precocious puberty.

PARAMETER	GNRH-DEPENDENT PRECOCIOUS PUBERTY	GNRH-INDEPENDENT PRECOCIOUS PUBERTY
Nature of puberty	Isosexual	Isosexual or heterosexual
Sequence of pubertal events	Similar to normal puberty	Disordered
Height velocity	Increased. Normal if coexistent growth hormone deficiency	Increased. Decreased in hypothyroidism
Cycles of breast growth and regression (girls)	Absent	May be present
Testicular size (boys)	Symmetric increase appropriate for pubertal stage	Prepubertal/asymmetric increase/symmetric increase but small for pubertal stage
GnRH stimulation test	LH peak in pubertal range	LH peak in prepubertal range
Common etiologies	Hypothalamic hamartoma, astrocytoma, previous encephalitis, radiation exposure, hydrocephalus	Congenital adrenal hyperplasia, adrenal neoplasm, hypothyroidism, McCune-Albright syndrome, familial testotoxicosis, exogenous sex steroid intake

Abbreviations: GnRH, gonadotropin releasing hormone; LH, luteinizing hormone.

- 2,4-dichlorophenol, a breakdown product of triclosan and a product of pesticide manufacturing
- 2,5-dichlorophenol, used in moth balls and room and toilet deodorizers
- Monoethyl phthalate, a metabolite of diethyl phthalate, a chemical used in personal care products with fragrance
- Methyl and propyl paraben, used as preservatives in cosmetics.

In our case, we are unable to measure endocrine-disrupting chemicals (EDC) and it was one of the limitations of our study.

In a retrospective study of 145 patients seen in Belgium during a 9-year period for treatment of precocious puberty, it prompts to the hypothesis that the etiology of precocious puberty could insinuate transient exposure to estrogenic endocrine disruptors.²⁰

In our case, we identify pesticides as a principal etiology of precocious puberty; they can be both estrogenic and antiandrogenic, and are used in home and for agriculture. Exposure is through food as well as through the skin.²¹

Conclusion

Even though the ability of the pesticides to behave as estrogen-like and androgens antagonist are low compared with the natural molecules, their capacity to act at several levels could boosting the biological outcomes in the normal organism.

As a result of our current lifestyle, we are exposed to different endocrine disruptors simultaneously, and all of studies have demonstrated that the action estrogenic-like compounds is additive and/or synergistic.^{22,23} Therefore, in the case of early life onset of precocious puberty without established cause, it is necessary to eliminate exposure to environmental xenoestrogen composites.

Author Contributions

AH wrote the manuscript, RE supervised the findings of this work, EFK supervised the findings of this work, RN supervised the findings of this work, DG supervised the findings of this work, BM supervised the findings of this work.

Patient's Consent

Informed consent has been obtained from the patient's parents for publication of the case report.

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