Review Article

Bulletin of Pure and Applied Sciences.
Vol.36 A (Zoology), Issue (No.1) 2017: P.23-30
Print version ISSN 0970 0765
Online version ISSN 2320 3188
DOI 10.5958/2320-3188.2017.00004.3

Precocious Puberty: A Review

Sharon Zulfiqar

Authors Affiliation:
Department of Zoology, University of Gujrat, Hafiz Hayat Campus, Gujrat, Pakistan

Corresponding Author:
Sharon Zulfiqar
Department of Zoology, University of Gujrat, Hafiz Hayat Campus, Gujrat, Pakistan.
E-mail:
sharonzulfiqar@hotmail.com
Received on15.03.2017
Accepted on 29.06.2017

Abstract

This study was conducted at Department of Zoology, University of Gujrat, Pakistan in 2017. The data regarding causes and effects of precocious puberty was obtained and compiled through a thorough review of various published research articles of international reputed journals and relevant books. Puberty results when pulsatile secretion of gonadotropin-releasing hormone (GnRH) is initiated and the hypothalamo–pituitary–gonadal (HPG) axis is activated. The onset of puberty is marked by breast development in girls and testicular enlargement in boys. The onset of puberty is affected by many factors in addition to race it occurs earlier in girls with early maternal menarche, low birth weight, or excessive weight gain or obesity in infancy and early childhood. The prevalence of precocious puberty is about 10 times as high in girls as in boys.

Keywords: Precocious puberty, pulsatile secretion, Gonadotropin-releasing hormone, maternal menarche, BMI

INTRODUCTION

Puberty is defined as the transition from sexual immaturity to sexual maturity. The two main physiological events that occur during puberty include the activation of the gonads by the pituitary hormones also known as “gonadarche” and the production of androgens by the adrenal cortex also known as “adrenarche.”

The initial clinical sign of female puberty is breast development, or thelarche, which normally occurs between the ages of 8 and 13 years. Early, or precocious, puberty (PP) in females is defined as the appearance of thelarche at an age 2.5–3 standard deviations (SD) below the mean age of onset of puberty [11].Girls are nearly 12 times more likely to develop precocious puberty when compared with their male counterparts [21].Girls with true precocious puberty, in addition to physical findings of thelarche and pubarche (pubic hair), have early growth

acceleration, pre- mature bone maturation, and initially become taller. Two classifications of precocious puberty include central precocious puberty (CPP), under the influence of pituitary control, or peripheral precocious puberty (PPP), which is secondary to estrogen production outside the influence of pituitary control.

PUBERTAL DEVELOPMENT

Pubertal development includes rapid growth of bones and muscles, changes in body shape and size, and development of the body's ability to reproduce. Marshall and Tanner [12] began documenting pubertal development more than forty years ago and identified five stages of pubertal development and physical elements of sexual maturity in boys (size of the testes, length of penis, pubic hair) and girls (breast and pubic hair development).

Table 1: Tanner-Scale Boys

Stages	Testis	Pubic hair	Penis stage	Other changes
1	Smaller than 4 ml or long axis < 2.5 cm	No coarse, pigmented hair	No growth	
2	Size 4 ml or long axis 2.5 to 3.2 cm. Age 11.5 years (age 9.5 to 13.5 years)	Minimal coarse, pigmented hair at base of penis Age 12.0 years (age 9.9 to 14.0 years)	Earliest increased length and width. Age 11.5 years (age 10.5 - 14.5 years)	
3	Size 12 ml or long axis 3.6 cm. Age 14.0 years (11.5 - 16.5 years)	Coarse, dark curly hair spread over the pubis. Age 13.1 years (11.2 - 15.0 years)	Increased length and width. Age 12.4 years (10.1 - 14.6 years)	• Gynecomastia (breast swelling) may occur (age 13.2 years) • Voice breaks (age 13.5 years) • Muscle mass increases
4	Hair of adult quality. Age 13.9 years (12.0 - 15.8 years)	Continued growth in length and width. Age 13.2 years (11.2 - 15.3 years)	Length 4.1 to 4.5 cm	• Axillary hair (age 14.0 years) • Voice changes (age 14.1 years) • Acne vulgaris (age 14.3 years)
5	Adult pubic hair distribution (15.3 years)	Mature genital size by 16.5 years	Length > 4.5 cm	• Facial hair present on sides • Mature male physique • Gynecomastia disappears

Table 1: In boys, genital development is rated from 1 (preadolescent) to 5 (adult); stage 2 marks the onset of pubertal development and is characterized by an enlargement of the scrotum and testis and by a change in the texture and a reddening of the scrotal skin. Pubic hair stages are rated from 1 (preadolescent, no pubic hair) to 5 (adult), and stage 2 marks the onset of pubic hair development.

Table 2: Tanner-Scale Girls

Tanner Stage	Pubic Hair	Breast
1	None	Papilla elevation
2	Minimal coarse, pigmented hair mainly on labia. Age: 11.2 years (9.0 - 13.4 years)	Small breast buds palpable and areolae enlarge. Age: 10.9 years (8.9 - 12.9 years)
3	Darker, begins to curl. Age: 11.9 years (9.6 - 14.1 years)	Elevation of breast contour; areolae enlarge. Age: 11.9 years (9.9 - 13.9 years)
4	Coarse, less curly than adult. Adult quality. No spread to junction of medial thigh with perineum. Age: 12.6 years (10.4 - 14.8 years)	Areolae forms secondary mound on the breast. Age: 12.9 years (10.5 - 15.3 years)
5	Adult triangle. Adult distribution of hair. Pubic hair spreads to medial thigh.	Mature; nipple projects. Adult breast contour. Areola recesses to general contour of breast.

Table 2: In girls, breast development is rated from 1 (preadolescent) to 5 (mature), and stage 2 (appearance of the breast bud) marks the onset of pubertal development. Pubic hair stages are rated from 1 (preadolescent, no pubic hair) to 5 (adult), and stage 2 marks the onset of pubic hair development.

DIFFERENTIATING CENTRAL AND PERIPHERAL PRECOCIOUS PUBERTY

Central Precocious Puberty (CPP) and Causes

The more common form of precocious puberty is central precocious puberty (CPP) wherein the entire hypo-thalamic-pituitary-gonadal axis (HPG axis) simply starts too soon [8, 12, 11]. As a result, very young girls may experience bodily signs of pubertal development and even menstruation.

Peripheral Precocious Puberty (PPP) and Causes

The second form is peripheral precocious puberty (PPP). In PPP, GnRH is not a factor. PPP could be due to a myriad of reasons because of ovarian cysts or other diseases of the ovaries, testicles, adrenal glands or pituitary gland [5]. In boys, gene mutation, a rare disorder, could also be a cause [1].

POSSIBLE CAUSES OF PRECOCIOUS PUBERTY

Medical Causes

Brain or spinal cord tumor or injury, hypothyroidism, congenital diseases of the ad- renal glands, bone genetic disease called McCune-Al- bright syndrome and radiation of the brain or spinal cord have been reported as causes (Anonymous 2011). Slyper [18] reported that the cause of early maturation could be due to hyper-insulinaemia (high insulin levels in the blood) and insulin resistance. Kaplowitz [6, 7] also reported an infection, such as encephalitis or meningitis, could be a cause of CPP.

Genetics

A genetic component may be linked to early pubertal development [15]. If there is a history of early puberty in a parent or sibling, it decreases the likelihood that early puberty has a medical cause.

Hormones in Milk and Meats

In the 1990's, the artificial bovine growth hormone, rBGH, was thought by some to be a stimulating factor but this is a protein hormone produced in cattle and is destroyed in human digestion. Additionally, rBGH is not a steroid hormone like estrogen [20].LH and FSH cause the ovaries to produce hormones involved in the growth and development of female sexual characteristics (estrogen) and the testicles to produce hormones responsible for the growth and development of male sexual characteristics (testosterone).

Environmental Factors

Parent [14] found that children, who exhibited signs of CPP, had the presence of DDT in their blood (plasma), a chemical that could disrupt endocrine function. Their subsequent experimental research demonstrated that DDT caused early maturation of rats. Plastics and insecticides were investigated as a cause of CPP because they break down into chemicals similar to estrogen. Among girls younger than seven, Colón, Caro, & Bourdony identified a compelling connection between exposure to phthalates and an increase in breast development [4].Environmental toxins are thought to be factors in the development of early / precocious puberty. The Federal Drug Administration (FDA) currently earlyand Precocious Puberty allows the use of six hormones in the food supply including many sex hormones: estradiol, estriol, testosterone, and progesterone. Estrogen storage in fat tissue increases the risk of over-weight children. Additionally, parabens, a known toxin, are found in everyday household items including soap, cosmetics, cleaning products, etc. The xeno-estrogens mimic estrogen in the body [10]. Buttke, Sircar, & Martin studied the association between the exposure of endocrine-disrupting hormones (EDC) and the age of menarche for girls aged 12 to 16 years old [2]. They found that 2, 5-dichlorophenol (2, 5-DCP) alone and in combination with 2, 4-dichlorophenol (2, 4 DCP) act as potential EDC's and were inversely associated with an earlier age of menarche (hazard ratios of 1.10; 95% CI: 1.01, 1.10 and 1.09; 95% CI 1.01, 1.19, respectively; P=0.025). The phenol 2, 5-DCP is a fumigant that is found in common household items such as mothballs, insect repellants, deodorizers, and toilet disinfectants.

Childhood Obesity

There is a relationship between increased body mass index (BMI) and body fat to early menarche, pubic hair, and breast development.Obesity was positively associated to early sexual development in girls but, in boys, obesity was associated negatively with sexual maturity [22]. Puberty requires the body to have a certain weight and fat distribution.Children who are overweight or obese have high levels of the protein leptin that can stimulate the release of the three main hormones in puberty: hypothalamic gonadotropin-releasing hormone, LH, and FSH. Lee, Kulin and Guo found that the rate of increase in body metabolism index (BMI) from age 3 - 6 years was positively associated with an earlier onset of puberty [11].

SIGNS OF PRECOCIOUS PUBERTY

In Girls

According to Kaplowitz, in girls, breast enlargement is seen first [6, 7, 8]. It may begin by occurring only on one breast. The breast diameter increases, the areola darkens and thickens and the nipple becomes more prominent.Pubic and axillary (underarm) hair may appear before breast development, at about the same time, or well after the appearance of breast tissue. If the clitoris appears large, it could indicate significant androgen (male hormone) excess. The color of the vaginal mucosa may go from deep- red color in pre-pubertal girls to moist pastel-pink.

In Boys

In boys, the first signs are testicular enlargement, which is due to an increased production of FSH that results in increased stimulation of testosterone.About a year later, the male child will experience penis growth, pubic hair growth, and reddening and thinning of the scrotum. Later, the child may acquire acne, voice change, and facial hair growth [6, 7, 8].

PROBLEMS ASSOCIATED WITH PRECOCIOUS PUBERTY

One major problem as a result of precocious puberty is that early growth spurts stop further growth. The brain signals the bones that growing time are over and children,therefore, instead of growing tall, will remain, on the average, shorter than their peers [6, 7].

Short Height

Children with precocious puberty may grow quickly at first and be tall, compared with their peers. But, because their bones mature more quickly than normal, they often stop growing earlier than usual. This can cause them to be shorter than average as adults. Early treatment of precocious puberty, especially when it occurs in very young children, can help them grow taller than they would without treatment.

Social and Emotional Problems

Girls and boys who begin puberty long before their peers may be extremely self-conscious about the changes occurring in their bodies. This may affect self-esteem and increase the risk of depression or substance abuse.

DIAGNOSTIC TECHNOLOGIES

Diagnosis includes blood tests to measure hormone levels. X-rays of the child's hand and wrist should determine the child's bone age and will show if the bones are growing too quickly. There are also specific procedures used to determine if early puberty is peripheral or central. Magnetic resonance imaging (MRI) of the brain may be done to assess if any brain abnormalities are causing the early start of puberty [2].

Magnetic Resonance Imaging (MRI)

A brain MRI is usually done for children who have central precocious puberty to see if any brain abnormalities are causing the early start of puberty.

Thyroid Testing

The doctor may also test your child's thyroid if he or she shows any signs of slow thyroid function (hypothyroidism), such as fatigue, sluggishness, increased sensitivity to cold, constipation, a drop in school performance or pale, dry skin.

TREATMENT

CPP (Central Precocious Puberty)

If the diagnosis is CPP, GnRH analogue therapy is given [1]. This requires a monthly injection of a medication, such as leuprolide, which stops the HPG axis and delays further development [2].

PPP (Peripheral Precocious Puberty)

If the diagnosis is PPP and is due to an underlying medical condition, that condition is treated. For example, if it's a tumor, it may need to be surgically removed [2].

ROLE OF KISSPEPTIN IN PRECOCIOUS PUBERTY

The onset of puberty is marked by an increase in gonadotropin secretion, which leads to sexual maturity and the ability to reproduce. Puberty can also be affected by a range of environmental factors, and is known to be affected by a person's metabolic capacity [16]. Gonadotropin secretion is brought about and regulated by gonadotropin releasing hormone (GnRH). GnRH leads to the release of luteinizing hormone (LH) and follicle stimulating hormone (FSH), which primarily target the gonads to trigger puberty and reproduction. The primary event that leads to the beginning of puberty is the activation of GnRH neurons. This event is thought to involve Kisspeptin/GPR54 signaling, which leads to the eventual activation of GnRH neurons [19]. Several studies have confirmed that addition of Kisspeptin to biological systems including rat, mouse, and sheep are able to bring about the release of LH and FSH. In addition to this, the release of these gonadotropins has proven to be dose dependent. A greater addition of Kisspeptin peptide resulted in greater release of LH and FSH. Kisspeptin was found to evoke one of the strongest effects on the gonadotropin system.

Kisspeptin's ability to stimulate the release of GnRH and gonadotropins is the result of its effect GnRH release at the hypothalamus. In rat hypothalamus, it was found that over three-fourths of GnRH neurons coexpress the receptor for Kisspeptin, GPR54, in their RNA. Kisspeptin was also able to bring about the release of GnRH both ex vivo and in vivo in rat and sheep. It can be concluded that by activating GnRH neurons in the hypothalamus, Kisspeptin causes GnRH release which leads to the release of FSH and LH. The major role Kisspeptin/GPR54 plays in sexual development was initially found in sexually immature humans and mice who had mutations that blocked the expression of the GPR54 gene [3]. In rats, the initiation of puberty accompanied a greater presence of KISS1 and GPR54 in mRNA. The same events were later observed in mammals, where KISS1 and GPR54 mRNA increased more than twofold in the hypothalamus. This suggests that there is greater expression of KISS1 and potentially even GPR54 at the onset of puberty leading to an increase in Kisspeptin/GPR54 signaling that results in the activation of the gonadotropin pathway. The addition of Kisspeptin to female rats who had yet to mature led to the initiation of gonadotropin pathway. In humans, it was shown that females at the beginning stages of puberty had much higher Kisspeptin levels than those females of the same age who had yet to begin puberty. It has been concluded that the activation of the GPR54/Kisspeptin pathway is a catalyst that leads to puberty onset [9].

ROLE OF ANTAGONIST OF KISSPEPTIN IN THE TREATMENT OF PRECOCIOUS PUBERTY

Kisspeptin-234 is a 10-amino acid peptide antagonist with potent neutral antagonist activity at GPR-54 and competes directly at the Kisspeptin-1 binding site. Kisspeptin-234 is the first reported antagonist for the kisspeptin-1/GPR-54 signaling system.

GPR54 (or KiSS-1R) is a G-protein coupled receptor that binds Kisspeptin and is expressed in the brain. Kisseptin-GPR54 signaling regulates gonadotropin-releasing hormone (GnRH) secretion. GnRH modulates the hypothalamic-pituitary-gonadal axis, enabling the brain to control reproductive processes. Kisspeptin-1 is a peptide neurotransmitter released from afferent neurons onto GnRH neurons, where it binds to and activates to the orphan receptor GPR-54 to regulate release of GnRH [13].

Role of GABA in the Mechanism of the Onset of Puberty

Evidence indicates that GABA is an inhibitory neurotransmitter responsible for restricting luteinizing hormone-releasing hormone (LHRH) release before the onset of puberty. LHRH neurons in the hypothalamus of female rhesus monkeys are already active during the

neonatal period, but subsequently enter a dormant state in the juvenile/pre-pubertal period because of an elevated level of GABA in the stalk-median eminence (S-ME). The developmental reduction in tonic GABA inhibition results in an increase in LHRH release in the S-ME, triggering puberty. The reduction in GABA also appears to allow an increase in glutamate release in the S-ME and this glutamate seems to further contribute to the pubertal increase in LHRH release [17].

CONCLUSION

Precocious puberty can be a troubling time for children and their parents, but fortunately there is medical treatment to stop further physical pubertal development, and there are several forms of support strategies available to help both the child and parents.

RECOMMENDATIONS

Parents, school nurses, and teachers should become knowledgeable about precocious puberty so that treatment and support can be given in the early stages.

REFERENCES

1. Anonymous. Mayo Clinic Staff (2011). Precocious puberty.
2. Antoniazzi, F. and Zamboni, G. (2004). Central precocious puberty: Current treatment options. Pediatric Drugs, 6:211-231.
3. Buttke, D.E., Martin, C., & Sircar.K. (2012). Exposures to endocrine-disrupting chemicals and age of menarche in adolescent girls in NHANES (2003-2008). Environmental Health Prespectives, 120(11), 1613-1618.
4. Colón, I., Caro, D., Bourdony, C., et al. (2000) Identification of phthalate esters in the serum of young Puerto Rican girls with premature breast development. EnvironmentalHealth Perspectives, 108:895-900.
5. Faizah, M., Zuharis, A., Zulfiqar, M., et al. (2012) Precocious puberty in children: A review of imaging findings.Biomedical Imaging and Intervention Journal, 8:1-8.
6. Kaplowitz, P. (2002). Precocious puberty in girls and the risk of a central nervous system abnormality: The elusive search for diagnostic certainty. Pediatrics, 109:139-141.
7. Kaplowitz, P. (2004). Clinical characteristics of 104 children referred for evaluation of precocious puberty. The Journal of Clinical Endocrinology & Metabolism, 89:3644-3650.
8. Kaplowitz, P. (2004). Precocious puberty: Update on secular trends, definitions, diagnosis, and treatment. Advances in Pediatrics, 51:37-62.
9. Kaplowitz, P. (2008). Link between body fat and the timing of puberty. Pediatrics, 121:
10. Landa, J. (2012). Hidden hormones can bring about early puberty in kids. Hidden-hormones-can-bring-about-early- puberty-in-kid
11. Lee PA, Kulin HE, Guo SS (2001). Age of puberty among girls and the diagnosis of precocious puberty. Pediatrics.107 (6):1493.
12. Marshall, W. and Tanner, J. (1969). Variations in pattern of pubertal changes in girls. Archives of Disease in Childhood, 44: 291-303.
13. Marshall, W. and Tanner, J. (1970). Variations in the pat- tern of pubertal changes in boys. Archives of Disease in Childhood, 45: 13-23.
14. Parent, A., Rasier, G., Bourguignon, J., et al. (2005). Early onset of puberty: Tracking Genetic and Environmental Factors. Hormone Research, 64:41-47.
15. Phillip, M. and Lazar, L. (2005) Precocious puberty: Growth and genetics. Hormone Research, 64:56-61.
16. Rhie YJ (June 2013). "Kisspeptin/G protein-coupled receptor-54 system as an essential gatekeeper of pubertal development". Annals of Pediatric Endocrinology & Metabolism. 18 (2): 55–59.
17. S208-S217.

18. Slyper, A. (2006). The pubertal timing controversy in the USA, and a review of possible causative factors for the advance in timing of onset of puberty. Clinical Endocrinology, 65:1-8.
19. Smith JT, Clarke IJ (March 2007). "Kisspeptin expression in the brain: catalyst for the initiation of puberty". Reviews in Endocrine & Metabolic Disorders. 8 (1): 1–9.
20. Styne D. (2011) Puberty. In: Gardner, D.G. and Shoback, D., Eds., Greenspan's Basic and Clinical Endocrinology 9th Edition, McGraw-Hill Medical, Chicago, 527-549.
21. Styne DM, Grumback MM (2011). Puberty: ontogeny, neuroendocrinology, physiology, and disorders. In: Melmed S, Polonsky KS, Larsen PR, Kronenberg HK, editors. Williams Textbook of Endocrinology. 12th ed. Philadelphia: Saunders Elsevier; p. 1054–201.
22. Wang, Y. (2002). Is obesity associated with early sexual maturation? A comparison of the association in American boys versus girls. Pediatrics, 110:903.