PedsCases Podcast Scripts

This is a text version of a podcast from Pedscases.com on "**Puberty and Pubertal Disorders – Part 2: Precocious Puberty.**" These podcasts are designed to give medical students an overview of key topics in pediatrics. The audio versions are accessible on iTunes or at www.pedcases.com/podcasts.

Pubery and Pubertal Disorders – Part 2: Precocious Puberty

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Introduction:

Hello! Welcome back to part two of our series on puberty and pubertal disorders. My name is Ruojin Bu, and I am a medical student at the University of Alberta. This series was created with the help of Dr. Elizabeth Rosolowsky, a pediatric endocrinologist at the University of Alberta.

Previously in part one, we examined the underlying physiology and clinical presentations of normal puberty. Now in this second episode, we will specifically discuss an approach to precocious puberty.

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By the end of this session, the learner should be able to:

1. Describe the clinical criteria for diagnosing precocious puberty
2. List the common causes of precocious puberty
3. Outline an approach for the common causes of precocious puberty

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In part one of our series, we were introduced to a 5-year 6-month old girl seen for concerns regarding the growth of pubic hair that started 6 months ago.

We observe that this girl is showing isolated growth of pubic hair with no breast development, so we deem that she is not going through TRUE puberty. But what could be the potential causes for isolated pubarche? Is 5 years of age too young to have Tanner stage 2 pubic hair?

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So what is early, or precocious, puberty?

Precocious puberty can be subdivided by the gonadotropin status, either gonadotropin-dependent or gonadotropin-independent.

Gonadotropin-dependent puberty is also known as Central Precocious Puberty. This refers to true puberty. The HPG axis is re-activated, the levels of gonadotropins – and particularly LH -- increase, stimulating the ovaries or testes to ramp up its production of sex steroids, and setting off the entire chain of pubertal events in a normal sequence. Because this is the sequence of events that happens in normal puberty, gonadotropin-dependent precocious puberty always occurs in an isosexual fashion, meaning that the physical manifestations are in line with the child's sex. In girls, we should only see signs of female puberty, like the start of breast development or menses. In boys, we should only see signs of male puberty, like an increase in testicular size. The sex steroids come from the gonads. So you can think of gonadotropin-dependent precocious puberty as being like "normal" puberty, only happening atypically early.

The other type that we have is the gonadotropin-independent precocious puberty, also known as peripheral or pseudoprecocious puberty. It's not true puberty because it is independent of the input from hypothalamus and pituitary, and the sex steroids may not be coming from the gonads. Gonadotropin levels are pre-pubertal or suppressed because of the negative feedback from sex steroids on the hypothalamus and pituitary gland. The sex steroids are made autonomously without any stimulating gonadotropins. These steroids can come from the gonads, the adrenal glands or other ectopic places in the body like the liver. There can also be an exogenous source, for example, medications. Because there is no regulation of sex steroid production by the gonadotropins, the physical manifestations of puberty can occur out of normal sequence. This means that a boy may achieve tanner IV pubic hair development without testicular enlargement; or a girl can have menstrual bleeding before breasts fully develop. The physical manifestations in peripheral precocious puberty can be isosexual or contrasexual. For instance, girls can have a male-pattern hair distribution like chest hair, and boys can develop gynecomastia, which specifically refers to breast development in boys.

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Clinically, gonadotropin-dependent precocious puberty is considered when the onset of breast development or thelarche occurs in girls younger than 8 years of age. In girls of African descent, their pubertal milestones are achieved earlier on average, so the cut-off is one year earlier -- younger than 7 years of age.

In boys, gonadotropin-dependent precocious puberty refers to testicular enlargement-growth of testes to 4 mL or greater in volume or 2.5 cm or greater in length-before 9 years of age.
At times, girls and boys may present with pubic hair and/or axillary hair, without breast development or testicular enlargement, respectively. If only hair appears before the age of 8 years for girls or before 9 years for boys, it is considered gonadotropin-independent or peripheral precocious puberty.

Here, the main distinction is that having only hair would not be central puberty; central puberty is suggested by breast development in girls and testicular enlargement in boys.

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Now when we look at the different causes of precocious puberty, we can describe them as gonadotropin-dependent, gonadotropin-independent, or as a normal variant.

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Let's begin with gonadotropin-dependent or central precocious puberty. Because it is gonadotropin-driven, we need to think about what is happening in the head. Are there any findings in the Central Nervous System (CNS) that could affect the hypothalamus or pituitary?
If we do find issues in the CNS, hypothalamic hamartoma is the most common cause. Hypothalamic hamartoma is a congenital, non-malignant mass in the brain, and we think that it contains an intrinsic GnRH pulse generating capacity. If there is a premature release of GnRH pulses, it could lead to the onset of precocious puberty. Other CNS lesions that you should consider include: tumors, cerebral malformations, and physical injuries to the CNS.

In the majority of clinical cases, however, we do not find any CNS lesions. Most often, we do not observe any findings at all, and we refer to this as idiopathic. Gonadotropin-dependent precocious puberty can also be related to genetics and international adoption, possibly due to an improved nutrition and weight gain after adoption.

For both boys and girls, the most common cause of central precocious puberty is idiopathic. However, and this is important to remember, boys are more likely to have a cause for their central precocious puberty; and if a cause is found, it is most likely to be a hypothalamic hamartoma.

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Now let's move on to gonadotropin-independent or peripheral precocious puberty. Here, the hypothalamus and pituitary are not activated to drive the secretion of GnRH and the gonadotropins. The sex steroids may arise from autonomous secretion from the gonads but the sex steroids may also come from elsewhere. Therefore, the secondary sexual characteristics exhibited may not be compatible with the child's sex.

Certain genetic disorders can lead to gonadotropin-independent precocious puberty. For example, in McCune-Albright syndrome, the gonads themselves can be activated autonomously to produce estrogen or testosterone. In testotoxicosis also known as familial male-limited precocious puberty, there is a mutation in the LH receptor leading to an increased production of sex steroids.

There could also be tumors in the gonads, liver or mediastinum that can rapidly sex steroids.

Peripheral precocious puberty can also be due to too much adrenal androgens being produced, notably congenital adrenal hyperplasia or CAH. In the most common form of CAH, we see a mutation of an enzyme involved in the synthesis of cortisol and aldosterone steroids in the adrenal glands. When there is a mild degree of enzyme deficiency, the body makes enough cortisol and aldosterone to not become acutely ill, but there is still an excessive amount of androgens. Mild forms of CAH are also known as non-classical CAH. Patients may present with pubic hair, axillary hair, and acne. Boys may also have increased growth of the penis. However, girls would not demonstrate breast development, and boys would not demonstrate testicular enlargement.

Another cause of peripheral precocious puberty to consider is an exogenous source of sex steroids, although this occurs much more rarely. For example, a boy or a girl may have had exposure to a family member's testosterone gel.

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The normal variants of precocious puberty are non-pathological and do not require any treatment other than observation and monitoring. The two common normal variants of precocious puberty that a pediatrician or family doctor are likely to encounter are premature thelarche and premature adrenarche.

Benign premature thelarche refers to an early onset of breast development, usually noted at 6-12 months of age. It is considered a normal variant because the hypothalamus and pituitary are still inactive, and the levels of GnRH and gonadotropins are undetectable in the blood. There is no pubic hair or any other secondary sexual characteristics present, and there is no acceleration in height, just as we would expect in other infants of the same age. Breasts remain small with little to no progression. The breast tissue should spontaneously disappear by 3 years of age.

Benign premature adrenarche refers to the growth of pubic hair usually before 8 years of age. In this condition, we only see the growth of pubic hair. There is no breast development for girls and no testicular enlargement for boys. There also is no height acceleration. The child may be in Tanner stage 2 based on the pubic hair.

It is important to stress here that these 2 entities are considered to be diagnoses of exclusion. The child must be followed over time to ensure there is no progression of puberty.

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Now that we have reviewed the different causes of precocious puberty, we will go over the approach to precocious puberty.

The first step in evaluating a child suspected of precocious puberty is taking a focused history. We need to know what the parents mean by "puberty." Do they mean just the hair growth, or breast or genital development? When were the findings first noted? How fast are they progressing? In addition, we need to check for the child's height and growth

velocity. If there is a rapid growth rate, this is concerning for a significant production of sex steroids which cause growth acceleration. In regards to family history, we need to ask the age of onset of puberty in parents and siblings, if applicable. We also need to delve into whether there are any signs or symptoms related to the brain suggesting increased intracranial pressure, such as headaches and/or visual impairment.

Next on the physical exam, we need to Tanner stage breasts in girls, genitals in boys, and pubic hair in both. We also need to look for any clinical signs of puberty, and any signs of contrasexual development. Does a girl have hirsutism, a male-pattern hair distribution? Does a boy have gynecomastia? If the child shows any contrasexual development, we should be considering causes of peripheral precocious puberty. To examine for CNS-related abnormalities, we can perform visual field testing and fundoscopic exam to look for signs of increased intracranial pressure.

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If there is increasing evidence of precocious puberty from a focused history and physical exam, we should consider appropriate lab investigations.
We can order a bone age to evaluate the effect of sex steroids on bone maturation. Children with precocious puberty generally have a more advanced bone age than their chronological age. We also measure the levels of sex steroids, and most importantly, the levels of gonadotropins. The measurements of gonadotropins should be done in the morning because they are initially produced in the body when a child is asleep and their levels wane throughout the day.

If we see an elevated level of LH and FSH that is normally seen during puberty, this strongly suggests a gonadotropin-dependent or central cause. We would then proceed to image the brain via MRI to look for any CNS lesions if there is reasonable suspicion. In general, it is recommended to obtain a pituitary MRI for all boys presenting with central precocious puberty because of the higher chance of significant lesions; and for girls less than 6 years of age or with rapidly progressing central precocious puberty.

Conversely, if we see that the levels of LH and FSH are undetectable, this directs us towards a gonadotropin-independent or peripheral cause. Then, we need to consider screening for non-classical CAH and look for tumors with ovarian, testicular or adrenal ultrasound.

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Let's now return to our case example.

From history and physical exam, we know that this 5-year 6-month old girl has isolated pubic hair growth. Her height and growth velocity appear normal. There is a family history of early growth of pubic hair as well. As you may recall, these features are more aligned with the clinical recognition of gondadotropin-independent precocious puberty. On physical exam, we do not appreciate any signs of contrasexual development or CNS abnormalities. Upon further investigation, we see that her bone age is not advanced, the level of androgens is mildly elevated, but the levels of gonadotropins remain suppressed.

Based on these results, we have increased our confidence in a gonadotropin-independent cause and we proceed to screen for non-classical CAH. We do not suspect a tumor because her androgen levels are not significantly elevated.

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Now let's conclude this video with a review of our learning objectives:

1. Describe the clinical criteria for precocious puberty
2. List the common causes of precocious puberty
3. Outline an approach for the common causes of precocious puberty

Thanks for your attention and be sure to check out part 3 of our series *An Approach to Delayed Puberty*.

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- Latronico AC, Brito VN, and Carel JC. Causes, diagnosis, and treatment of central precocious puberty. *Lancet Diabetes Endocrinol* 2016; 4(3): 265-274.