Precocious Puberty

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Faculty Disclosure

- Faculty: Laura Stewart
- No relationships with commercial interests

Objectives

- To review causes of pubertal changes that present earlier than normal
- An approach to investigation and management of children with early puberty
- To review cases of children presenting with early pubertal changes
- Determine which presentations of early pubertal development require prompt investigation and management
Definition of Precocious Puberty
- Puberty with an onset prior to age 7 in girls and age 9 in boys
- Menarche prior to 9.5 years of age
- Complete precocious puberty refers to activation of the hypothalamic-pituitary gonadal axis
- Incomplete puberty is either isolated breast development or pubic hair development

Initiation Of Puberty
- Leptin levels increase as puberty nears and it is needed for the initiation of puberty
- As the adiposity increases, so do leptin levels
- This explains the fact that overweight girls enter puberty earlier and may also explain the secular trend for earlier puberty

Benign Variants of Early Pubertal Development
- Premature Thelarche
- Premature Adrenarche
- Constitutionally Early Puberty
Central Precocious Puberty

- Early activation of the hypothalamic-pituitary-gonadal axis prior to age 6 in girls is often associated with rapid pubertal progression
- Those with an onset after age 6 in girls and after 8 in boys often have a gradual pubertal progression and preserved adult height
- The cause is idiopathic in 95% of girls
- Boys often have an identifiable cause

Central Precocious Puberty

- Neurological disorders such as hydrocephalus and epilepsy can be associated with CPP
- Hypothalamic hamartomas often are associated with puberty that begins at a very young age
- Other tumors (astrocytomas, CNS germ cell tumors, ependymomas) may cause CPP
- The “inhibitory neurons” are damaged by cranial irradiation

Central Precocious Puberty

- Activation of the hypothalamic-pituitary-gonadal axis can occur after conditions resulting in chronic sex steroid exposure are treated
- This seen in children with CAH, McCune-Albright syndrome, Familial Gonadotropin-Independent Sexual Precocity
Incomplete Puberty: Thelarche

- Benign premature thelarche
- Functional Ovarian cysts
- McCune–Albright syndrome (activating mutation of the α-subunit of the G protein)
- Granulosa cell ovarian tumours
- Exogenous estrogen exposure
- Severe primary hypothyroidism
- It may be the first sign of CPP

Isolated Pubarche In Girls

- Benign premature adrenarche
- Congenital adrenal hyperplasia
- Adrenal adenomas or carcinomas
- Masculinizing ovarian tumors (leydig-sertoli cell tumors)
- Exposure to exogenous androgens
Males With Peripheral Androgen Production

- Benign premature adrenarche
- Congenital adrenal hyperplasia
- Androgen-secreting adrenal tumours
- Testicular tumours (leydig-cell, interstitial cell tumours)
- HCG-secreting tumours

Males With Peripheral Androgen Production

- Familial gonadotropin-independent sexual precocity (AD sex-limited disorder secondary to a mutation of the LH receptor @ the G protein-binding domain)
- McCune-Albright syndrome (rare)
- Exogenous androgen exposure

Approach To Children Presenting With Early pubertal Changes

- Obtain a history of the onset and progression of puberty
- Exposure to exogenous sex steroids
- Symptoms of increased intracranial pressure & associated neurological problems
- Symptoms of adrenal insufficiency
- Tanner staging (including testicular volume in boys)
Precocious Puberty: Investigations
- In children with minimal pubertal changes or those who are presenting within the early normal timing of puberty, clinical follow-up may be all that is needed
- LH, FSH & sex steroid levels
- GnRH stimulation test may be needed
- Bone age
- In documented gonadotropin-dependent puberty, a cranial MRI is needed

Isolated Pubarche: Investigations
- Check cortisol and 17-hydroxyprogesterone levels between 0730 and 0800 hours
- An ACTH stimulation test may be needed
- DHEAS, Testosterone
- In boys, an HCG level is useful
- If there is gonadotropin-independent puberty and CAH is ruled out, an adrenal or testicular ultrasound may be needed

Isolated Thelarche: Investigations
- In girls who are in the infant to 2 year-old range and have mild thelarche, clinical follow-up is all that is needed
- Gonadotropin, estradiol levels, +/- GnRH test
- Bone age
- TSH
- If there is gonadotropin-independent puberty, a pelvic ultrasound may be needed
Central Precocious Puberty: Treatment

- Medical intervention is not needed in children with slowly progressive puberty or those with onset later than 6 years in girls or 8 in boys
- These families need reassurance
- They need information explaining the pubertal process and ways to help their child deal with the changes
- There are good resources for children and parents that explain pubertal changes

Central Precocious Puberty: Treatment

- GnRH agonists are used in children with rapidly-progressive CPP
- For girls who start puberty prior to 6 & boys beginning prior to age 7-8, there is evidence that GnRH agonists improve adult height as well as suppression of puberty
- For those with peripheral puberty, the underlying condition needs to be treated

Case: Jada

- Jada is a 28 month old girl who has bilateral breast development
- He mother feels that the tissue has been there for 4-5 months and it has not progressed significantly
- There is no pubic or axillary hair development
- There is no vaginal bleeding or discharge
- She is otherwise well
Case: Jada

- On examination, her height is 90.5 cm (50%), weight 13.3 kg (75%)
- Her general examination is normal
- She is Tanner 2 for breast development and stage 1 for pubic hair development

Case: Jada

- LH <0.2 IU/L, FSH 4.2 IU/L, estradiol 52 pmol/L
- The bone age was 2 10/12 years

Case: Jada

- She has benign premature thelarche
- This condition is associated with delayed suppression of the hypothalamic-pituitary gonadal axis
- There is often a history of waxing and waning of the breast size
- Usually clinical observation is all that is required
Case: Tina

- Tina is a 29 month old girl who was referred because of early pubertal changes
- She was noted to have breast development at 24 months of age
- She was noted to have blood in her diaper at 26 months of age
- At 28 months, she had 3 days of vaginal bleeding

Case: Tina

- On physical examination, her height is 108 cm (>98%) and weight 18.7 kg (>98%)
- She has a normal general examination
- She is Tanner stage 3 for breast development and 1 for pubic hair development

Case: Tina

The bone age was 5 9/12 years.

<table>
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<th>FSH (U/L)</th>
<th>Estradiol</th>
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<td>9.0</td>
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Case Tina
- She has central precocious puberty
- Her MRI scan shows a hypothalamic hamartoma
- She is managed with Lupron Depot
- The breast tissue regresses
- She has no further menses

Case: Joan
- Joan was referred because of early pubertal development
- At 4 4/12 years she had breast development followed by brown vaginal discharge and then menses, lasting for 2 days
- It progressed rapidly over 2 weeks
- The breast development regressed

Case: Joan
- She had a second episode 3 months later
- The breast development progressed rapidly
- Menses occurred 1 week later and lasted for 5 days
- Her height is 113 cm (>95%) and weight is 25.4kg (>95%)
Case: Joan

Her general physical examination was normal
She is Tanner 3 breast, Tanner 1 pubic hair development
She has 2 café au lait spots. One was 0.5 cm in diameter and was located on her right forearm and the other was 0.6 cm and was on her abdomen

Case: Joan

The bone age was 6 10/12 years

GnRH Stimulation Test

<table>
<thead>
<tr>
<th>Time</th>
<th>LH (U/L)</th>
<th>FSH (U/L)</th>
<th>Estradiol</th>
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<td>40</td>
<td>&lt;0.1</td>
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Case: Joan

A pelvic ultrasound shows multiple large ovarian cysts on both ovaries
A skeletal survey shows multiple areas of polyostotic fibrous dysplasia
Ovarian Cysts
- The estrogen levels climb rapidly & are often high
- There often is dark pigment around the areola and labia minora
- When the cyst resolves, menses can occur
- Large cysts can lead to ovarian torsion
- Girls with recurrent cysts may have MAS

McCune- Albright Syndrome
- Cafe Au Lait spots
- Fibrous dysplasia of bone
- Peripheral precocious puberty
- It can be associated with other endocrinopathies

Case: Joan
- She has McCune Albright Syndrome
- Aromatase inhibitors are somewhat effective
- She will need ongoing monitoring for pathological fractures
Hayden
- He is a 4 10/12 year old boy who was referred for pubic hair development and acne
- He has never been hospitalized
- He is on no medication
- There has been no growth spurt
- There is no family history of early puberty, virilization or unexplained deaths

Case: Hayden
- His height is 116.2 cm (97%ile), weight 24 kg (97%ile)
- BP 93/55
- His general examination is normal
- He is Tanner 3 for pubic hair development
- The testicular volume is 2 mL

Case: Hayden
- The bone age is 7 10/12 years
- Sodium 138 mmol/L, potassium 4.1 mmol/L
- His cortisol is 265 nmol/L @ 0750 h
- The 17-hydroxyprogesterone is 16.9 nmol/L

ACTH Stimulation Test

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<th>Cortisol</th>
<th>17-OHP</th>
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<td>298</td>
<td>378</td>
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Case: Hayden
- He has simple virilizing 21-hydroxylase deficiency
- He is treated with hydrocortisone replacement

Case: Alison
- Alison is 7 years of age and has a 6 month history of pubic and axillary hair development
- She may have some breast development
- She has not had menarche
- There is no access to estrogen or androgen-containing medication
- She has been overweight for the last 4 years
- Her height remains on the 75%ile

Case: Alison
- Her height is 125 cm (75%ile) and weight 42 kg (>97%ile), BMI 26.9 kg/m2 (>97%ile)
- Her general examination is normal
- She has acanthosis nigricans
- She is Tanner 1 for breast development but has a significant amount of adipose tissue in the breast area
- She is Tanner 2 for pubic hair
### Case: Alison
- Her bone age is 8 10/12 years
- DHEAS 3.9 umol/L
- Testosterone 0.4 nmol/L
- Cortisol 498 nmol/L @0755 h
- 17-OHP 4.6 nmol/L @0755 h
- Fasting glucose 5.3 mmol/L
- Fasting Insulin 256 pmol/L

### Case: Alison
- She has benign premature adrenarche
- The DHEAS is appropriate for her pubic hair stage
- She does not have CAH
- Central puberty usually begins at a normal time
- This condition is often the first sign of the metabolic syndrome

### Case: Sarah
- Sarah is 7 years, one month of age and presents with a 10 month history of rapid weight gain
- She also had pubic and axillary hair development that has progressed
- She has hirsutism which has been treated with laser therapy for 6 months
- There is no voice change
Case: Sarah

- There is breast development but she has not had menarche
- She continues to grow normally
- She has no symptoms suggestive of adrenal insufficiency
- She is on no medications.
- Her past history is unremarkable

Case: Sarah

- Her height is 126.2 cm, weight 33.5 kg, BP 135/80, heart rate 98
- She has no dysmorphic features
- There is generalized obesity and the appearance of increased musculature
- Her general examination was normal
- She had severe acne

Case: Sarah

- There was moderate hair growth involving the side-burn area, upper lip, chin, neck, chest and abdomen
- She is Tanner 5 for pubic hair development and Tanner 2 for breast development
- She has mild clitoromegaly
Case: Sarah

- Sodium 140 mmol/L, potassium 4.2 mmol/L
- Glucose 8.4 mmol/L
- TSH 1.2 mU/L, free T4 12.8 pmol/L
- DHEAS 22.4 umol/L
- Free testosterone 8.9 pmol/L
- ACTH < 1.0 pmol/L, cortisol 890 nmol/L, 17-OHP 8.9 nmol/L @ 1730 h
- LH 1.2 U/L, FSH 1.2 U/L, estradiol 51 pmol/L

Case: Sarah

- A 24 hour urine collection showed a cortisol of 1670 nmol/L, creatinine 11.8 mmol/L
- The morning cortisol after 1 mg of dexamethasone was 780 nmol/L
- The abdominal ultrasound showed a right adrenal mass

Case: Sarah

- Sarah has a virilising adrenal tumour
- These tumours are often malignant
- She needs imaging to rule out metastases
- The curative treatment is surgical excision of the adrenal gland that harbors the tumor
Adrenocortical Tumors

- These tumors can present in young children
- They may present with features of Cushing syndrome but often present with virilization, especially if malignant
- The progression of the virilization is often rapid
- There may be associated breast development in some children secondary to aromatase action on the androgens

Features of Pathological Causes of Early Puberty

- Young age of pubertal onset
- Rapidly progressive puberty
- Evidence of virilization such as clitoromegaly or significant hirsutism
- Significant growth spurt and/or advanced bone age
- Associated neurological abnormalities