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 (astrocytomomas, CNS germ cell tumors, ependymomomas) 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
Cortisol and Aldosterone Biosynthesis

- **Cholesterol** → **Pregnenolone** → **17-OH-pregnenolone** → **Dehydroepiandrosterone**
- **3β-Hydroxysteroid dehydrogenase (3βHSD)**
  - **Progesterone** → **17-OH-progesterone** → **Androstenedione**
    - **21-hydroxylase**
      - **Deoxycorticosterone** → **11-deoxycortisol** → **Testosterone**
        - **11-β-hydroxylase**
          - **Corticosterone** → **Cortisol**
            - **18-hydroxylase**
              - **18-OH-corticosterone** → **Aldosterone**
                - **18-oxidase**
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.
- Her 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.

**GnRH Test**

<table>
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<tr>
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<th>LH (U/L)</th>
<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

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

Figure 2. McCune-Albright Syndrome (case 2). A: Hand/wrist x-ray showing epiphyseal dysplasia. B: Café-au-lait macule on the face. C: CT scan showing a well-defined hyperdense lesion with a dense peripheral capsule. D: Forearm radiograph showing a hyperdense trabeculae with ground-glass appearance; note calcification seen with well-defined halo in the anterior mandible region. E: Hemangiopericytoma of fibrous connective tissue with thin discontinuous calcification bone trabeculae. F: Multiple cafe au lait macules on upper lips.
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 116.2cm (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>Time</th>
<th>Cortisol</th>
<th>17-OHP</th>
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<tbody>
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<td>13.7</td>
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<tr>
<td>60</td>
<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 75th percentile.
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/d
- 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