Growth and Puberty: A clinical approach

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NOTHING TO DISCLOSE
Why is this character short?
LINEAR GROWTH IN BOYS CONCEPTION TO ADULTHOOD
Genetic potential

- Food
- Psychosocial factors
- Major Systems (+drugs)
- Perinatal
- Classical Hormones
  - "Endocrine"
- Growth Factors
  - "Endocrine/Paracrine/Autocrine"
Hormones through the life cycle

- Prenatal
- Birth
- Neonatal period
- Childhood
- Puberty
- Adult
- Senescence
What initiates puberty?

- Gonad independent increase in GnRH release
- Balance between inhibitory and excitatory inputs to the approx 1000 GnRH secreting neurones
- Complex neuronal networks
- Glial cells also modify inputs, via secretion of growth factors

**Transsynaptic:**
- Inhibitory pathways: GABA, enkephalin
- Excitatory: glutaminergic, Kiss-1

**Glial:** Excitatory only
What initiates puberty?

• Nutrition

• Genetic Factors

• Skeletal Maturity
Clinical Pubertal Assessment

• Tanner Stages
  - Breast
  - Pubic Hair
  - Genitalia
  • Testicular volume
Case 1

- What do you think about this growth chart?
- What else would you like to know to assess the patient?
Normal Variants

- Genetic/Familial Short stature
- Constitutional Delay of Growth and Development
# Normal Variants: GV normal

<table>
<thead>
<tr>
<th></th>
<th>Familial</th>
<th>Constitutional Delay</th>
</tr>
</thead>
<tbody>
<tr>
<td>Height</td>
<td>&lt; -2 S.Ds</td>
<td>&lt; -2 S.Ds</td>
</tr>
<tr>
<td>Bone age</td>
<td>=chronological</td>
<td>&lt;chronological</td>
</tr>
<tr>
<td>Puberty</td>
<td>Normal</td>
<td>Delayed</td>
</tr>
<tr>
<td>Growth Velocity</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Final Height</td>
<td>Short</td>
<td>Normal/Tall</td>
</tr>
<tr>
<td>Parents</td>
<td>Short</td>
<td>Normal</td>
</tr>
<tr>
<td>Family History</td>
<td>Positive (for short stature)</td>
<td>Positive (for constitutional)</td>
</tr>
</tbody>
</table>
Case 2

• What is this well known character short?
Hypopituitarism

- 60 years old
- History of x 50 head injuries!
- Immature appearance
- Rippled central obesity
- Proportionate short stature

CMAJ • 2004; 171 (12):1433
Pathological Causes: GV abnormal

- **Other Systems**
  - Subclinical GI/renal disease
- **Psychosocial (neglect)**
  - History
- **Small for gestational age**
- **Genes**
  - Turner syndrome
  - Skeletal dysplasia
  - Syndromes
Pathological Causes

• **Hormones**
  - Thyroid deficiency
  - Growth hormone deficiency
  - Glucocorticotoid excess
  - Combinations: Pituitary
    - Congenital (eg septo-optic dysplasia)
    - Acquired (Eg tumour, irradiation, significant head injury)

• Hypothalamus

• Any simple clinical clues to these?
  • Short and Fat
Approach

• **History**
  - Height measured accurately and over time
  - Mid-parental height
  - Perinatal history
  - Past history (including previous significant head injury, surgery, drugs, etc)
  - Family history
  - Systems
  - Psychosocial
  - Development
Approach

• Examination
  - Growth parameters (auxology)
  - Dysmorphic features
  - Proportions
  - Blood pressure
  - Fundi and visual fields
  - Thyroid (goitre, hypothyroidism)
  - General (chronic disease with limited symptoms)
Investigation

• **Bone Age**

• *Other investigations depend on your clinical assessment and particularly growth velocity*

• *All girls with significant short stature require a karyotype*
Treatment

• Treat the cause
• **Growth hormone**
  - Growth hormone deficiency
  - Turner syndrome
  - Chronic renal failure
  - Intrauterine growth retardation
  - Prader Willi Syndrome
  - Severe idiopathic short stature (trial)
• **Androgens**
  - Consider in constitutional delay
Case 3: Miss CB - 2.5 year old girl

- What do you think about this growth chart?

- What else would you like to know to assess the patient?
Growth in Turner Syndrome

• **Short stature is one of the commonest things that happens in Turner syndrome**
  - Most girls are short
  - Almost all girls are short for their family
  - Important growth genes on the X-chromosome (esp SHOX gene)

• **Altered tempo of growth**
C.B.
Turner syndrome
45,X/46,Xi(Xq)
What can we do about Growth?

• Growth hormone therapy
  - Lots of studies have shown that growth hormone improves the speed of growth and final height
  - The earlier it starts the better the long-term effect
  - Dose of growth hormone is also important
  - With early start can normalise final height

- Additional benefits: Bones, timing of puberty
Recent developments with growth


• Randomised study in 150 girls age 5-12.5 years with 4 groups:
  - Placebo
  - Very low dose estrogen
  - Growth hormone
  - Growth hormone plus very low dose estrogen

• (Type of estrogen used no longer available)
Results

• **Growth hormone treatment improved final height by around 5 cm**

• **Additional very low dose estrogen added further 2.2 cm to this**
  - Relatively late therapy in some of the girls
  - Given 3 times a week rather than daily (less effective)

• **Toddler study: JCEM 2007, Davenport ML, Quigley CA.**
  - Early growth hormone therapy corrects the early growth impairment in Turner syndrome
• Low dose estrogen also appeared to improve some other things:
  - Speed of processing some information
  - Motor function
  - Memory
C.B.
Turner syndrome
45,X/46, Xi(Xq)
Progress

• She is now 12 years old

• What should we do about puberty?
Pubertal Induction

• Somewhere between 5 and 25% of do commence puberty spontaneously (depending on chromosomes)
  - Usually doesn’t progress
  - Need to see a high FSH before starting

• Most girls will need pubertal induction or estrogen supplementation at some point
Timing

• Balance: Growth (delaying a bit gives you longer to grow)
• Being on par with peers (aim for usual timing of puberty)
• Uterine development
  – Improves chances of carrying a pregnancy

• Individual decision. Early growth hormone treatment generally means you can start this sooner (on par with peers), but with late diagnosis sometimes worth delaying
• Ideally start before 14 to maximise uterine growth
How to do it?

• **Mimic natural puberty**
  - Slowly increasing doses of estrogen over 2.5-3 years
  - Progesterone later in the process (cyclical)
    • Normal menstruation
    • Healthy endometrium
  - Initially very low doses
    • Symmetrical breast development

• **Type of estrogen: As natural as possible**
  - Oral, transdermal, combined
Transdermal Estrogen

- **Matrix patches (estrogen imbedded in a membrane applied to skin)**
  - Can cut the patch to a very small size, which allows the right dose to be given

- **Evidence that topical estrogen leads to better uterine growth than oral estrogen**

- **Special Authority limits for topical estrogen**
- **Occasionally not tolerated because of skin reactions**
Outcomes

• Feminisation
• Uterine growth
• Healthy Bones (acquisition of bone mass)
• Cessation of growth
• Miss CB has now completed puberty and is 16 years old

• Are there any other issues you should think about as her GP?
Transition to adulthood

• Moving on to adult life healthy
• School/Learning
• Bones
• Hearing
• Heart
School/Learning

- Addressing individual learning needs throughout childhood
- Specific learning issues
- Practical assistance with important exams
- Addressing anxiety, etc
Bones

Normal

Osteoporosis
Bones

• Obtain maximal peak bone mass
  - Healthy nutrition
  - Exercise (weight bearing)
  - Growth hormone
  - Estrogen

• Monitoring (DXA at end of puberty)

• Maintain Bone Health (Prevent excess loss of bone)
  - Healthy nutrition (incl dietary vitamin D and calcium/phosphate)
  - Exercise (weight bearing)
  - On-going estrogen (continuous).. Probably not the OC

• Early Diagnosis therefore critical
Hearing

• Screening for sensorineural hearing loss
Heart

- Monitoring of Blood Pressure

- Reassessing heart/major blood vessels
  - ECHO and/or MRI
  - Critical if contemplating pregnancy
Case 4: 5 year old girl

• What do you notice on the following slides and what would you do about it?
• Premature thelarche (benign) verses true precocious puberty

• When should puberty start?
Normal Pubertal Variants

- Neonatal “Mini-Puberty
- Premature Thelarche
- Premature Adrenarche
- Gynaecomastia
Why is this character short?
Turner syndrome

- Linda Hunt
Summary - take home points

• Most growth and pubertal disorders can be sorted out with a standard clinical approach
  - Normal variants of both growth and puberty are common. Pathological causes are less common but have clinical clues
  - Bone age is very useful (don’t do lots of tests)

• Measure children’s heights as well as weight when they come to see you
  - Previous measurements and calculation of growth velocity is often the most important thing

• Turner syndrome is not uncommon, is multi-systemic and needs follow-up/anticipatory guidance across the whole life cycle
  - Do a karyotype in any girls below 5th centile or with additional clinical features
More Reliable Height Measurement

- Appropriate measuring device (stadiometer)
- Calibrate frequently (before and after each session)
- Single trained observer (yourself)
- Careful positioning of child (stretch gently)
- Measure without reference to previous heights
- Measure at beginning and end of examination