Update on Practical Paediatric Endocrinology

Kyriaki Sandy Alatzoglou
Department of Paediatric Endocrinology
Chelsea & Westminster Hospital
Aims

Practical approach for investigation and management of:

- Growth disorders in childhood
- Delayed or early puberty
- Thyroid problems in children
- Case discussion
The ICP growth pattern

- **Infancy**
  HV 8-12 cm/yr;
  Period of ‘catch up’ or ‘catch down’ growth usually completed by 18 mo.

- **Childhood**
  HV 5-7 cm/yr, relatively constant until the onset of puberty

- **Pre-pubertal deceleration**

- **Puberty**
  Sex specific differences in tempo and magnitude.
  Mean difference in adult height between men and women: 13-14 cm.

Nutrition; contribution from GH minimal

Thyroid

Sex steroids

Thyroid

GH

GH


Height velocities in boys and girls

- Later onset of puberty in boys
- Two additional years of pre-pubertal growth
- Extra 8-10 cm of growth pre-pubertally
- Greater amplitude of pubertal growth (3–5 cm)

PHV
Females 8.3 cm/yr (6.2-10.4)  
6-9mo after B2
Males 9.5 cm/yr (7.2-11.7)  
TV10 ml
Approach to the short child

• Is growth rate normal or abnormal?  
  Regular measurements & plotting  
  Calculation of HV, is it normal for age?  
  Mid-parental and target height  
• Is there abnormal tempo of growth?  
  Pubertal staging  
  Bone age  
• Are there underlying reasons?  
  History including family history  
  Chronic illness  
  Findings from clinical examination
Short, no disproportion

Low HV and weight

- Systemic disease (respiratory, CVS, GI, Nutritional, Renal, Infections, Rheumatoid disorders, Neurological)

Low HV and weight appropriate or relatively high

- Hypothyroidism
- GHD
- Hypopituitarism
- Pseudo-hypoparathyroidism

Normal HV

- Familial short stature (appropriate for parents)
- Constitutional delay
Short, dysmorphic

Recognisable syndrome

- Low birth weight: RSS, Seckel
- Chromosomal: Turner, Prader-Willi
- Autosomal dominant: Noonan
- Autosomal recessive: Fanconi, Bloom syndrome
- Rare: Kabuki make-up syndrome

Limb-trunk disproportion

- Short limbs: ACH, HCH, multiple epiphyseal dysplasia, chondrodysplasia
- Short limbs and trunk: Metatropic dysplasia
- Short trunk: Mucopolysaccharidosis Spondyloepiphyseal dysplasia

From Brook’s Clinical Paediatric Endocrinology 6th edition
## Clinical approach

### Examination
- Ht, Wt, HC
- Systemic examination
- Signs of chronic disease
- Midline structural abnormalities (cleft, single central incisor)
- Eye abnormalities (microphthalmia, anophthalmia, ONH)
- Fundoscopy
- Visual fields, acuity
- Pubertal staging
- Signs of psychosocial/emotional deprivation

### Investigations
- FBC, CRP, ESR
- U&Es, LFTs and Bone Profile
- Thyroid function tests
- Coeliac screen
- IGF-1/IGFBP-3
- (Depending on age: LH/FSH, Oestradiol/Testosterone, depending on age)
- Karyotype (girls)
- X-ray of non dominant hand and wrist (assess skeletal maturity, BA)
- Growth hormone stimulation tests
- Pituitary Imaging
Case 1.

Boy referred at 9.8 yrs
Ht 122cm
Pre-pubertal
No systemic problems

Term
SVD, BW on 50th centile
No neonatal problems

From previous data, calculated
HV 2.8cm/yr

Q: Normal or abnormal? investigations
Investigations

1st line

FBC and baseline chemistry normal
Coeliac screen negative

FT4  17.9 pmol/L (n)
TSH  1.6mU/L (n)

IGF-1  <25 ng/ml
IGFBP-3  1.15mg/L

Dynamic pituitary function test and Imaging

Glucagon test

Peak GH 3.0 µg/L
Peak Cortisol 1067 nmol/L
PRL 249 nmol/L

LH basal 0.7
LH peak 3.4
FSH basal 0.3
FSH peak 1.7

MRI : hypoplastic anterior pituitary
Case 2.

- 4 year old boy
- Referred from urologist for short stature
- Ht<3rd centile, short for parents
- HV 3.5cm/yr

- Baseline: U&Es, LFTs, FBC normal
- FT4  6.5pmol/L
- TSH  1.5mU/L
- Insufficient sample for IGF-1

What to do next....
Case 2

- Ensure adequate cortisol
- Cortisol 8am 255nmol/L
- Treat hypothyroidism
- GH provocation test once euthyroid
- Peak GH 4.5µg/L
- GHD
- MRI: structural pituitary abnormality, ectopic PP
- Surveillance for other pituitary hormone deficiencies
Septo-optic dysplasia

Two of:
(i) Optic nerve hypoplasia
(ii) Pituitary hormone deficiencies
(iii) Midline defects (agenesis/dysplasia of septum pellucidum and/or corpus callosum)

• 1 in 10000 live births

Webb EA & Dattani MT. Eur J Hum Genetics 2010 18(4):393-7
Pitfalls in the diagnosis and monitoring of congenital hypopituitarism

➢ Low TSH/ Secondary hypothyroidism will be missed by neonatal screening

➢ Need to ask for symptoms/history of hypoglycaemia from neonatal period

➢ SOD associated with precocious puberty (hypothalamic dysfunction) or hypogonadotrophic hypogonadism (LH and FSH deficiency).

➢ Ask about fluid intake
Measure paired fasting plasma and urine osmolalities
May need water deprivation test to confirm diagnosis of DI.
SGA

- Definition: BW or/and length <-2SDS (or below third centile)
- Majority show catch up growth within 1-2 years
- 8-10% of SGA children may not demonstrate catch up growth by the age of 4 years
- Short stature relative to their peers and MPH.
- Insulin resistance in later life is well described in SGA infants.

- rhGH licensed for children with growth failure at 4 years or older and who were born small for gestational age (NICE)
- Height <-2.5 SDS or <-1SDS below MPH,
- Height velocity <0 SDS.
Summary 1.

- Assessment of short stature is at multiple levels:
  History, exclude chronic/systemic illness, physical examination, detailed auxology, biochemistry, endocrine investigations, imaging, genetics

- Assess growth in association with HV, MPH, pubertal status

- Be aware of association of eye defects/ONH/SOD with growth failure and pituitary hormone deficiencies

- Be aware that pituitary hormone deficiencies may evolve over time
Trends in puberty

Girls

- Precocious < 8yrs (B2)
- Delayed > 13yrs
- PHV B2-3
- Menarche BA 13yrs
  - Fat mass 17%
  - (22% for regular cycles)

Boys

- Precocious < 9yrs (G2 testes > 4ml)
- Delayed > 14yrs
- PHV T10mls

For puberty to occur need minimum BMI 17kg/m²
Pubertal disorders

- Delayed
- Early
- Arrested
- Discordant
- Central and peripheral causes
## Delayed puberty - Basal LH & FSH

<table>
<thead>
<tr>
<th>Low</th>
<th>High</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Constitutional delay (CDGP)</td>
<td>• Primary gonadal causes</td>
</tr>
<tr>
<td>(Bone age delayed)</td>
<td>Turner</td>
</tr>
<tr>
<td>• Systemic/reversible causes</td>
<td>Klinefelter</td>
</tr>
<tr>
<td>(Chronic illness, anorexia, thyroid</td>
<td>XY gonadal dysgenesis</td>
</tr>
<tr>
<td>problems)</td>
<td>Autoimmune</td>
</tr>
<tr>
<td>• Central Hypogonadotrophic Hypogonadism</td>
<td>Androgen insensitivity</td>
</tr>
<tr>
<td>(Sense of smell, midline defects)</td>
<td></td>
</tr>
</tbody>
</table>
Delayed puberty

• **History**
  Progress/pattern, chronic illness, medication, eating disorders, activity, smell, sings/symptoms of pit hormone deficiencies, hx of orchidopexy, social/emotional/developmental hx, family

• **Systemic examination**
  Syndromic features, fundoscopy, visual fields, midline defects

• **Auxology**
  Ht, Wt, HV, MPH, THR (target height range) and *Pubertal stage*

• **Bone age**

• **Imaging**
  US (uterine size, lining, ovarian volumes), MRI (central lesions)

• **Biochemistry**
  Baseline chemistry
  Basal LH/FSH, Testosterone/ Oestradiol
  TFTs, PRL
  Karyotype
Case

- 9 year old boy
- Term, SVD, BW 3.5kg
- Concerns about stature
- Mild asthma
- Ht on 0.4th centile
- Follows centile
- BA 8.1yrs (at 10yrs)
- Initially dx as constitutional delay, puberty may be late
- Back at 14yrs
- Delayed puberty, TV <4ml
- Ht <0.4th
- Testosterone low dose, 6 months
- Reassessment, Tv 6ml
- Normal progress through puberty with appropriate growth spurt
CDGP

- Delayed sexual maturation
- Complex inheritance, clusters in families
- Short stature but appropriate for skeletal maturation
- HV normal for pre-pubertal
  
  5cm/yr at 12yrs

  Decline by 1cm/yr for each year puberty delayed

- Investigation: **Bone age**
- Differential from HH/central causes
CDGP vs HH

- Retrospective analysis of 43 boys: 29 CDGP, 14 HH
- GnRH test and 3d and 3wk HCG test
  - Peak 3d Testo: 3.6 nmol/l
  - Peak 19d Testo: 9.5 nmol/L

Segal et al, JCEM 2009;94:780-5
Case

13 yr old boy, with delayed puberty
HV plateau last 2 years
Ht -3.0SDS, Wt -1.0SDS
G1P1A1 T2/3
Investigations from previous hospital reported:
Normal U&Es/FBC/ESR/CRP, negative coeliac
TFTs : FT4 9.1pmol/L (9-24), TSH 1.1mU/L (0.4-4.4)
IGF-1 insufficient sample
Peak GH to glucagon 3mcg/L

Any comments?
Early/precocious puberty

**Consonant (B/G/HV)**

- Central (Gonadotrophin dependent)

**Idiopathic**
- Hypothalamic hamartoma,
- Cranial irradiation
- Brain Neoplasms
- Optic glioma
- NF1
- CP
- Congenital/SOD

**hCG-producing neoplasms, low gonadotrophins**
- (germ cells tumours)

Recent identification of genetic causes
Early pubertal development, not consonant

<table>
<thead>
<tr>
<th>Category</th>
<th>Conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gonadotrophin independent (loss of normal feedback, LH/FSH low, abnormally functioning receptor)</td>
<td>McCune Albright Testotoxicosis</td>
</tr>
<tr>
<td>Abnormal pattern of gonadotrophin secretion (ie isolated breast development)</td>
<td>Premature thelarche Thelarche variant Hypothyroidism</td>
</tr>
<tr>
<td>Adrenal androgens</td>
<td>Adrenarche, CAH Cushing’s disease Adrenal tumours</td>
</tr>
<tr>
<td>Androgen excess/virilisation</td>
<td>CAH Adrenal neoplasms</td>
</tr>
<tr>
<td>Gonadal sex steroids</td>
<td>Leydig cell tumours, Granulosa cell tumours</td>
</tr>
<tr>
<td>Exogenous sex steroids</td>
<td>Environment/medicines</td>
</tr>
</tbody>
</table>
Early puberty

- **History**
  Progress/pattern, family hx

- **Systemic examination**

- **Auxology and pubertal staging**
  Age at start, tempo of puberty, how quickly is it progressing

- **Biochemistry**
  Basal LH/FSH
  Testosterone/ Oestradiol
  TFTs,
  Androgen profile (17OHP, A4, DHEAS)
  Other depending on clinical context such as:
    - GnRH test
    - Urinary steroid profile
    - Synacthen test
    - Urinary free cortisol

- **Bone age**

- **Imaging**

Pelvic US (uterine size, lining, ovarian volumes)
MRI (central lesions)
Testicular enlargement due to activation of the LH/HCG receptor
Premature adrenarche

• Signs of an increase in androgen action (pubic hair development, body odour, oily hair and skin) before the age of 8 years in girls and 9 years in boys.

DDx:
• Mild or non-classical forms of CAH (0-40% depending on selection cohort)
• Androgen secreting tumours
• Cushing

Investigations
Auxology
Bone age
Baseline androgen profile (17OHP, A4, DHEAS)

2nd line: Synacthen (cortisol, 17OHP, 11DOC)
    USP
Premature thelarche

- Isolated breast development (uni or bilateral)
- Usually young age (<2 years)
- Self resolving
- Maintains pattern of growth
- Normal progress to puberty
- Expected adult height

- Baseline gonadotrophins: FSH dominant response
Should we always treat central precocious puberty?

Consider:
- Progression (rapid vs slow)
- Adult height potential
- Psychological issues

- Clinical criteria for GnRHa treatment:
  - If documented progression of pubertal development.
  - If accelerated growth velocity and skeletal maturation (features of sustained and/or rapidly progressing CPP)

- Many patients with CPP have a slowly or non-progressive form and achieve adult height within their target range without GnRHa
- Some patients with slowly progressive CPP may have advanced bone age and will reach normal AH without intervention
Case

• 7 yr old girl
• 3 episodes of vaginal bleeding
• No breast development, axillary or pubic hair
• Normal Ht, Wt, HV
• Basal LH, FSH low
• E2 low
• US prepubertal uterus, no endometrial stripe
• GnRH test prepubertal response
Isolated menarche

- Girls 4-8yrs
- No sings of precocious development
- Pelvic US +/- GnRH test

- Exclude other causes:
  Foreign body
  Vulvovaginitis
  Abuse
  Trauma
  Tumours (rhabdomyosarcoma)
Hyperthyroidism

• Graves' disease; 0.1 per 100,000 children
• 3.0 per 100,000 adolescents per year.
• 10-15% of thyroid disorders in children

• 1st line anti-thyroid drugs

• Frequency of relapse is higher in children than in adults

• Remission in only 30% of children after a first course of treatment for about 2 years.
Case

- 12.5 yr old girl
- Ht 150.4cm (25<sup>th</sup>-50<sup>th</sup>), wt 38.4 (25<sup>th</sup>)
- Referred by GP, tired, puffy eyes, hand tremors
- Initial investigation by GP FT4>100, TSH<0.01
- Started: Carbimazole 30mg OD and Propranol 10mg TDS and referred to endo clinic
- Seen 3 three weeks after initial presentation: HR 104, diffuse smooth goiter
Grave’s disease in children

- Cohort of 154 children with GD treated with Carbimazole for 24 months
- Relapse rate: 59% at 1 year post end of treatment
  - 68% at 2 years post end of treatment
- Risk higher for: non Caucasian (2.5x)
  - high TSH receptor antibodies
  - high FT4 at diagnosis
  - young age at diagnosis
- Risk decreases with increasing age of onset, and duration of first course of ADT
- TRAbs remained elevated in 36% of those measured at end of treatment

Kaguelidou F et al. JCEM 2008;93:3817-3826
# Case 7: Results/investigations

<table>
<thead>
<tr>
<th>Test</th>
<th>D0</th>
<th>Oct</th>
<th>Nov</th>
<th>Jan</th>
<th>Feb</th>
<th>April</th>
<th>1yr</th>
<th>2yr</th>
<th>Range</th>
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<tbody>
<tr>
<td>FT4</td>
<td>&gt;100</td>
<td>8.8</td>
<td>17.7</td>
<td>17.1</td>
<td>25.5</td>
<td>8.02</td>
<td>17.1</td>
<td>17.7</td>
<td>9-23</td>
</tr>
<tr>
<td>FT3</td>
<td>NA</td>
<td>6.7</td>
<td>13.7</td>
<td>12.4</td>
<td>17.4</td>
<td>NA</td>
<td>NA</td>
<td>NA</td>
<td>2.5-5.7</td>
</tr>
<tr>
<td>TSH</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>&lt;0.05</td>
<td>&lt;0.01</td>
<td>0.014</td>
<td>&lt;0.05</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Carbimazole (mg)</td>
<td>30</td>
<td>20</td>
<td>20</td>
<td>20</td>
<td>30</td>
<td>25-20</td>
<td>15-20</td>
<td>5-15</td>
<td></td>
</tr>
</tbody>
</table>

US: diffuse, enlarged thyroid, no nodules

Anti TPO (+): 314 (0-75u/ml)
Anti TSH receptor antibodies (+): 6.8 u/ml (0-0.4)
http://www.marsipan.org.uk/
Thank you

"By God, for a minute there it suddenly all made sense!"