**DEFINITION**

Puberty: A complex developmental process that begins in late childhood and is characterized by maturation of the HPG axis resulting in the appearance of secondary sexual characteristics and increased growth.

Precocious Puberty: The appearance of secondary sexual characteristics and increased growth at an age that is earlier than normal.

Based on a cross sectional data obtained in 1960, designated normal age range of pubertal onset as between 8 to 13 yrs in Females and 9 yr 6mon to 13yr 6mon in Males.

Based on a study done in US, included 17000 Girls looking at age of onset of puberty. In 1999 the Lawson Wilkins Pediatric Endocrine society recommended lowering the normal age of onset of puberty from 8 to 7 yrs in white female and to 6 yrs in African-American Females.

**PREVELANCE**

- Affects 1 in 5,000 – 10,000 children
- More common in Females (F/M=10/1)
- Over past 30 yrs incidence of PP in on the rise.

**OBJECTIVE**

- DEFINITION/ PREVELANCE
- PHYSIOLOGY
- FORMS OF PRECOCIOUS PUBERTY
- THERAPY
- CASES

**PRECOCIOUS PUBERTY**

ZOUL MENHEM

PEDIATRIC ENDOCRINOLOGY
Physiology of HPG axis

- Onset of puberty caused by an increase in the amplitude and frequency of GnRH release.
- Increased spikes of LH and FSH.
- Control of Hypothalamic GnRH synthesis and secretion result from a balance between stimulatory and inhibitory neurotransmitters

- Acetylcholine
- Catecholamine
- GABA
- Opioid peptide
- Prostaglandins
- Serotonin

Other substances:
- Neuropeptide Y
- B Endorphin
- Leptin
- Glutamate
- Kisspeptine

PHYSIOLOGY

GONADOTROPIN DEPENDENT PRECOCIOUS PUBERTY

- Idiopathic CPP
  - Diagnosed by exclusion
  - Most common cause in girls
    - 85% of cases of CPP
  - In males (consider CNS lesion)
- Risk factors
  - Adopted children from developing countries
  - Nutritional factors
  - Ethnicity
  - Psychosocial factors
  - Inaccuracies in age
GDPP

- CNS abnormalities
  - Space occupying lesions
    - Hamartoma, Optic gliomas (NF1), Astrocytomas and Ependymomas
  - Anomalies
    - Empty sella syndrome, subarachnoid cysts and midline defects
    - Hydrocephalus
    - Abscess
    - Cerebral damage
      - Head trauma
      - Cranial irradiation
      - Meningitis / encephalitis
      - Surgery

HAMARTOMA

- A nonneoplastic congenital malformation
- A heterotropic collection of hypothalamic tissue
- Located in base of the brain, floor of third ventricle
- Contains neurosecretory neurons
  - LHRH or TNF alfa (stimulus for LHRH release)
  - Acts as ectopic GnRH pulse generator
  - Increase in pulsatile gonadotropins (LH& FSH)
- 2-28% of patient with GDPP have hypothalamic hamartoma
- MRI of Brain
  - Non enhanced mass of similar intensity to normal hypothalamic tissue

GONADOTROPIN INDEPENDENT PRECOCIOUS PUBERTY

- Numerous etiologies
- Increased circulating sex steroids
  - Independent of HPG axis
    - Adrenal glands
    - gonads
- All can cause
  - Short stature
  - Psychosocial stressors

GONADOTROPIN INDEPENDENT PRECOCIOUS PUBERTY

- Girls:
  - Ovarian cysts
    - Follicular cysts most common cause of GIPP
  - Ovarian tumors
    - Rare
    - Granulosa cell tumors and gonadoblastoma
GONADOTROPIN INDEPENDENT PRECOCIOUS PUBERTY

Boys:
- Leydig cell tumor
- Asymmetric testicular enlargement
- hCG secreting germ cell tumors
  - Secretes hCG → activates LH receptors on Leydig cell → testosterone
  - Liver tumors (hepatoblastoma)
  - Choriocarcinomas of gonads, mediastinum, retroperitoneum and pineal gland
- Testotoxicosis

GONADOTROPIN INDEPENDENT PRECOCIOUS PUBERTY

Both sexes can present with:
- Adrenal cause
  - Adenomas or carcinomas
  - Enzymatic defects (CAH)
- Exogenous sex steroids
  - Androgen (cream/ointment)
  - Estrogens (BCP)
  - Anabolic steroids
- McCune-Albright Syndrome
- Primary hypothyroidism (Van Wyk-Grumbach syndrome)
  - TSH is similar to LH in structure
  - Binds to LH receptors
  - Leads to growth arrest

CLINICAL PRESENTATION

**In Girls**
- Breast development
- HT velocity
- Pubic / Axillary hair
- Acne
- Oily skin & hair
- Voice
- Mood behaviour

**In Boys**
- Testicular enlargement
- Penile enlargement
- Pubic / Axillary hair
- Acne
- Muscle mass
- Voice
- Mood behaviour
- HT velocity
EVALUATING PATIENT WITH PP

- Good history
  - Age of onset of puberty
  - Rate of progression of puberty
  - Growth velocity
  - Hx suggesting CNS dysfunction
    - Headache
    - Visual impairment
    - Seizure
  - Hx of exposure of sex steroid

- FMH
  - Age of onset of puberty
  - Calculate MPH
    - Male (F+M +13/2)
    - Female (F+M -13/2)
  - Genetic disorders (Testotoxicosis)

PHYSICAL EXAM

- Complete PE
- Careful description of secondary sexual characteristics:
  - Acne
  - Oily skin and hair
  - Body odour
  - Muscle development
- Tanner staging, genital exam
- HT, WT velocity (growth chart and cm/yr)
- Neurological exam, Fundoscopy
- Visual fields
- Neurocutaneous stigmata (Cafe au Lait)
- Careful Abdomen and Pelvic palpation for masses

LABORATORY INVESTIGATION

- Basal levels of LH and FSH
  - Not very helpful (pulsatile)
- GnRH stimulation test (Gold standard)
- Male
  - Testosterone levels
  - hCG (hCG secreting tumors)
- Female
  - Estradiol
- Both sex test for
  - TSH, FT4, DHEAS, Androstendion and 17 OHP

Tanner Staging

**DIAGNOSTIC IMAGING**

- **BONE AGE (Greulich and Pyle atlas)**
  - Shows skeletal maturation in relation to age
  - Useful for baseline and for comparison
  - Determining final HT
- **ULTRA SOUND Abdomen/Pelvic**
  - Document adrenal, testes, ovarian and uterine size
- **MRI OF HEAD indication**
  - Evidence of neurological or ophthalmologic deficit
  - Puberty at young age
- Bone scan (MAS)

**PREMATURE THELARCHE**

- Appearance of unilateral/bilateral breast development
- Benign condition
- Occurring from birth to 3 yrs of age
- Spontaneous regression within months or persists to puberty
- BA=CA
- HT velocity is normal
- LH, FSH, Estradiol prepubertal levels
- FSH N/inc
- Up to 18% can progress to complete CPP
- Close F/U assessing progression of puberty
  - HT velocity repeat BA if needed

**PREMATURE ADRENARCHE**

- Appearance of pubic and axillary hair
  - Female < 7-8 yrs
    - Absence of breast development
    - Up to 20% will develop CPP
  - Male < 9 yrs
    - Absence of testicular development
- Associated to adrenal androgen production
- NL HT velocity
- Must R/O CAH
- Female are at future risk for PCOS
- No treatment needed

**PREMATURE MENARCHE**

- One or more episodes of vaginal bleeding
- Occurring between age 4-8 yrs
- No breast development
- No abnormal
  - Physical finding
  - Hormonal studies
    - Gonadotropin and estradiol levels are prepubertal
    - Diagnostic imaging
    - S & H CA
- Must R/O
  - Foreign body
  - Vulvovaginitis
  - Sexual abuse
  - Tumor
**McCUNE-ALBRIGHT SYNDROME**

- Triad of Precocious Puberty, Cafe au lait skin lesions and Polyostotic Fibrous Dysplasia of Bones.
- F>M
- Gain of function mutation in GNAS1 gene for alfa subunit of stimulatory G protein.
- Constant stimulation of LH receptors
- Pubertal levels of Estradiol / Testosterone
- Prepubertal Gonadotropin levels (LH,FSH)

**MAS**

- Cafe aux lait skin lesion (90%)
  - Irregular borders
  - Present at birth
  - Single/multiple lesions
- Polyostotic fibrous dysplasia (60%)
  - Involve long bones and skull
  - Cystic like area of bone reabsorption
  - Bone pain, fractures and deformity

**MALE LIMITED PRECOCIOUS PUBERTY (TESTOTOXICOSIS)**

- Sporadic
- Autosomal dominant disorder 90% penetrance
  - Located on chromosome 2
- Presenting with precocious puberty in males
  - Activating mutation on LH receptor gene→ premature Leydig cells maturation and secretion of testosterone
- Girls not affected because need both FSH and LH for estrogen synthesis
TESTOTOXICOSIS
Clinical Presentation
- Onset of symptoms early in life 1-4 yrs of age
- Increased penile growth
- Axillary and pubic hair
- Acne
- Increase in HT velocity
- BA advance
- Testicular enlargement
- Aggressive behaviour
- Spontaneous erections

TESTOTOXICOSIS
DIAGNOSIS
- Pubertal levels of testosterone
- Prepubertal LH and FSH levels (basal and stim)
- BA is advanced
- Testicular biopsy (not needed)
  - Leydig cell maturation and hyperplasia
  - Some spermatogenesis
- Family Hx – males with PP
- Genetic testing - available

TESTOTOXICOSIS
TREATMENT
- Agents that inhibit androgen synthesis
  - Decreasing Testosterone levels
    - Cyproterone acetate and Medroxyprogesterone acetate
  - Ketoconazole
    - Inhibition of steroidogenesis
      - CYP-450 enzyme 17,20-desmolase
      - 11,17 and 18-hydroxylase
    - Side effect is hepatotoxicity
- Aromatase inhibitor
  - Testolactone
  - anastrasole
- Androgen receptor blocker
  - spironolactone

TESTOTOXICOSIS
Morbidity:
- Short stature if untreated
- Treated patients can develop secondary CPP
  - Pubertal LH response to GnRH stim. test
  - GnRH analog should be added to treatment
**PREOCIOUS PUBERTY TREATMENT**

- Depends on etiology
- Underlying cause
  - Tumors (surgical, chemo or radiation)
- Decision to treat is dependent on
  - Rate of sexual maturation
  - Estimated adult HT

**THERAPY FOR GDPP**

**Past Treatment:**
- Medroxyprogesterone acetate or cyproterone acetate reduce gonadotropin secretion by negative feedback.

**Current Treatment:**
- GnRH agonist IM once monthly
  - Dose of 3.75 mg or 7.5 mg
  - Other forms: SC, daily, intranasal insufflations; SC implants yearly.
- Down regulate GnRH receptors
  - Decrease in Gonadotropin and Sex steroids
  - Cause rapid stopping of pubertal development

**Side Effects:**
- Allergic reaction
- Headaches
- Local inflammation
- Local pain at site of injection

**THERAPY**

- Complete suppression of gonadotropin secretion is necessary
- Incomplete suppression
  - BA advances
  - Growth rate decreases
  - Result in Adult short stature
- Suppressive effect is reversed after therapy is discontinued

**THERAPY**

- Psychological support:
  - Sexual precocity
  - Somatic changes
  - Impact of menses
  - Social maturation to match their physical development
  - Treated as older because of their size
  - Increased risk of sexual abuse
  - Patient and family need supportive counselling
**THERAPY**

- When to stop treatment
  - Based on retrospective analysis suggestion to stop treatment at age 11 yrs is associated with optimal outcome.
- Pubertal progression reappear within months of stopping GnRH (~6mon)
- Mean time to Menarche is 16 months
- Long term fertility (not fully evaluated but preliminary observation are reassuring)

**CASE 1**

- 4.5 yr old F with Breast development
- At 2 yrs of age had similar episode of:
  - Breast development
  - Axillary / pubic hair
  - One episode of spotting
- Lab:
  - LH <0.1
  - FSH <0.3
  - TSH 2.44
  - Lyts: Na 140, K 3.9
  - RBC 4.8
- DI
  - MRI - NL
  - US Pelvic - Ovarian follicles with one dominant

**Case 1**

- Now 4.5 yrs:
  - Breast development
  - HT velocity – NL
  - No Acne, Oily skin or hair
  - No Spotting
- PMH: Unremarkable
- FMH:
  - Mother 5.0 ft
  - had similar Hx at age 2 yrs
  - Menarche age 14 yrs
  - Father 6.0 ft

**Case 1 Physical Exam**

- HT 75%, WT 60%
- Unremarkable, No cliteromegaly
- Pubertal development
  - Pubic hair T 2
  - Breast T 3
Case 1
- BA 60 yr, CA 40 yr
- Late CHILD APPEAR
- Bone age 9, 10, 11 yr
- Test: E 25, 40, 60, 90
- FSH 40 38 30 30
- LH 10 15 10 10
- Estradiol < 37
- Plan: close 70 in Simon
- Patient showed regression of symptoms
CASE 2

T

2 yr old M referred for precocious puberty

Family noticed 6mon Hx of:
- Pubic hair
- Testicular size
- Penis size
- HT velocity increased from 25% to 75%
- Deeper voice
- Oily skin/hair

PMH:
- Unremarkable
- Mild Asthma (Puff PRN)
- No Androgen exposure

FMH:
- Parents of average HT
- Maternal uncle diag. with T
- Maternal 1st cousin diag. with T

PE:
- Unremarkable, WT 90%, HT 75%
- Pubertal development
  - Pubic hair T 2
  - Testes 4 ml
  - Penis 7 cm stretched
  - Scrotum hyperpigmented

Work Up

By Family Doctor:
- LH <1
- FSH <0.3
- Test. 5.0
- TSH 2.25

BA =36mon, CA=34mon

Case 2

GnRH stim test:

<table>
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<th>LH</th>
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<tr>
<td>60</td>
<td>1</td>
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</tbody>
</table>
Case 2

- Treatment:
  - Ketoconazole po daily

Testotoxicosis

CASE 3

- 28-month-old female
- During routine physical at pediatrician
- Increased breast development
  - Time of onset unknown
- Increased HT velocity (noted by mother)
- No Hx of:
  - Axillary/pubic hair
  - Acne
  - Oily skin/hair
  - Bleeding
- Bone age
  - CA = 23 mon → BA 30 mon

PMH:
- UTI at age 10 mon
- Deny exposure to estrogen

FMH:
- Mother GDM and PCOS
- + FMH for T2DM

PE: unremarkable
- HT and WT at 90%
- Pubertal development
  - Breast T3
  - No axillary/pubic hair
CASE 3
Work Up

- GnRH stim test
  - Time: 0 20 40 60
  - LH: <1 69 49 41
  - FSH: 4 29

- US OF PELVIC
  - Bilateral ovaries with dominant follicles seen
  - Estrogen stimulated uterus

- MRI OF BRAIN
  - A 3 mm Hypothalamic Hamartoma

Female with Isolated Breast Development

CASE 3
HAMARTOMA

Female with Virilization and no breast development
REFERENCES

1. Update on the Etiology, Diagnosis and Therapeutic Management of Sexual Precocity (Arq Bras Endocrinol Metab 2008; 52/1:18-31)


