Central Precocious Puberty:  
To Treat or Not to Treat and Other Clinical Dilemmas  
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Objectives
- Describe potential pharmacologic options for treating patients with central precocious puberty and identify appropriate use of these medications
- Discuss current practice styles and potential ways to either maintain or change current styles based on current research data

Defining Puberty
- Hormonally mediated transition between childhood and adulthood
- Goals of puberty
  - Development of secondary sexual characteristics
  - Achievement of adult height
  - Reproductive maturity
- Requires interaction between hypothalamus, pituitary, gonads, and internal sexual organs
Sequence of Puberty

Average American Girls

Average American Boys


Pubertal Growth Spurt

Girls' peak growth rate: 11.5 years
Boys' peak growth rate: 13.5 years


Pubertal Milestones with Growth Spurt Overlay

Sexual Development: Girls

Sexual Development: Boys

Pubertal Milestones

- **Female**
  - Breast Development - 10 years
    - Range: 8-13 years
  - Sexual Hair - 11 years
    - May proceed breast development (10%)
  - Menarche - 12.5 years

Physical Exam: Tanner Stages

- **Male**
  - Testicular Enlargement - 11 years
    - Range: 9-14 years
  - Sexual Hair - 12 years
    - May proceed testicular enlargement

Resist describing children with "unitary Tanner stages"
What is Precocious Puberty?

- **Females**
  - Breast development before age 8 years old

- **Males**
  - Testicular enlargement before age 9 years old

Precocious Puberty (PP) Evaluation

- Physical exam!
- Diagnostic studies – first line
  - Gonadotropins
    - Morning ICMA (ultrasensitive) LH and FSH
  - Estradiol/testosterone
  - Bone age
- Diagnostic studies to consider:
  - GnRH/GnRHa stimulation testing
  - Thyroid Function Tests (TFTs)
  - MRI of pituitary gland

Central Precocious Puberty (CPP)

- **Girls**
  - Most often idiopathic (85%)
  - Physically and hormonally normal except for age of onset
  - Intracranial disorders (impair normal childhood suppression of hypothalamus)
    - CNS tumors (astrocytomas, gliomas, germinomas)
    - Myelomeningocele
    - Congenital anomalies (hamartomas)
    - Trauma
    - Postsurgical or postradiation
Central Precocious Puberty (CPP)

- Boys
  - More likely to be pathologic (up to 60%)
  - Also can be idiopathic

Potential Reasons to Treat with a GnRH Agonist

- Compromised Adult Height
- Psychosocial and Behavioral

Treatment for CPP

GnRH Agonist Treatment

- Leuprolide (Lupron)
  - 3 month injection vs. monthly injection
  - IM injection
  - Cost: $8,936-$17,868 per year
    - Does not include cost to administer
  - Administered at PCP’s office or Endocrinologist’s office
Treatment for CPP
GnRH Agonist Treatment

- Lupron Depot Dosing (1-month formulation):
  - <25 kg: 7.5 mg
  - 25-37.5 kg: 11.25 mg
  - >37.5 kg: 15 mg

- Lupron Depot-Ped® (3-month formulation):
  - 11.25 mg
  - 30 mg

- Annual histrelin implants (Supprelin):
  - Hydrogel implant delivery system
  - FDA approved for CPP in the US in 2007
  - Inserted under skin with brief sedation in surgery clinic
  - Releases histrelin for year
  - Replaced about every 12 months, prn
  - $16,800/year
  - Does not include cost to place and remove

- Supprelin Dosing
  - 50 mg for children 2 years of age and older
How Do GnRH Agonists Work?

- Low dose of continuous exposure vs. pulsatile GnRH
- Initial stimulatory effect, followed by suppression due to GnRH receptor insensitivity

GnRH Agonist Treatment

What to Expect

- Initial stimulatory effects
- No further breast development/testicular enlargement or potential regression
- Decrease in growth velocity
- No effect on pubic hair

Side Effects of GnRH Agonist

- Injection site reaction
- Hot flashes
- Weight gain
- No significant long-term effects
  - Decreased bone mineral density
- Normal puberty returns on average 16 months after completion of therapy
Case Study: Annie
Clinical Presentation
► 5 years 4 months old female
► Tanner 3 breast development, Tanner 2 pubic hair
► Linear growth at 95th%ile
  • Increase in growth velocity?
► Family history of early puberty

Case Study: Annie
Evaluation
► TFTs normal
► Gonadotropins not completed as ordered
► Stimulation testing confirmed CPP – peak LH of 5.8 mIU/ml
► Bone age advanced by 2 years
► MRI of the pituitary gland normal

Case Study: Annie
Treatment
► Treated for psychosocial reasons and height preservation!
► 5 years 6 months treatment with Leuprolide 11.25 mg monthly
  • By 4 months s/p start of tx, PE is stable
  • Stimulated LH shows suppression!
► 6 years 4 months treatment switched to Leuprolide 11.25 mg 3 month depot
  • 15 months later bone age has progressed by 12 months
  • Stimulated LH remains suppressed at 0.796 mIU/ml after 2nd injection
Case Study: Peter
Clinical Presentation

Evaluation

- Gonadotropins
  - ICMA LH and ICMA FSH pubertal
  - Stimulation testing not needed
- Testosterone in pubertal range
- Bone age advanced by 3 years 6 months
- MRI of the pituitary gland revealed a hamartoma
Case Study: Peter
Treatment
► Peter successfully treated with Lupron monthly

Potential Reasons to Treat
with a GnRH Agonist
► Compromised Adult Height
► Psychosocial and Behavioral
So What’s the Dilemma?

- Treatment for CPP is not always so clear cut
  - Will this treatment (with a GnRH agonist) make my child taller?
  - What is the best length of treatment with a single Supprelin implant?
  - Other potential dilemmas?

Will This Treatment (with a GnRH agonist) Make My Child Taller?

Case Study: Nicole

Clinical Presentation

- Nicole is a 7 years 6 months old female with precocious puberty
- Parents report breast development within the past 6 months
- Family history is positive for CPP – mom was 9 years 6 months old at menarche
Case Study: Nicole

Evaluation

- Baseline LH is 0.4 with estradiol of 3 pg/ml
- Height is at the 5th percentile
- Bone age advanced by about 18 months and predicts final height of 59"
- Mid-Parental Height (MPH) is 61"

Will treatment make Nicole taller?


- Greatest height gain in girls <6 years
  - 9-12 cm
- Girls between 6 and 8 years MAY have a moderate benefit
  - 4.5 ± 5.8 to 7.2 ± 5.3 cm
  - Therapy should be individualized
- Insufficient data in boys
  - Consider in all boys before 9 years

A Further Look at the Research...
Dutch Experience

- Height gain was 11.7cm, 7.9cm, and 6.1cm, respectively for < 6 years, 6-8 years and > 8 years


German Experience

- Height gain of 5.5 ± 1.4 cm for entire group
  - Height gain in Group 1 (< 6 years) was significantly higher than Group 2 (9.5 ± 2.3 cm vs 1.6 ± 1.0 cm)


NIH Experience

- For 6-8 years of age, average adult height was 6.8 ± 6.9 cm greater than pretreatment predicted height
- Over half (48 of 91) of children came within 5 cm of target heights
- Careful evaluation of girls between 6-8 years of age – tempo!


The Research Continues and So Do the Similar Findings

Research Studies


Similar findings

- Modest height gain (4.5 - 7.2 cm) for 6-8 year old females
- Treatment in kids 6-8 years old might not be warranted
Case Study: Will Treatment Make Nicole Taller?

Factors to Consider for Treatment
- Chronologic age
- Starting bone age
- Starting height
- Age of puberty
- Tempo of puberty
- Duration of potential treatment

What is the Best Length of Treatment with a Single Supprelin Implant?
Supprelin Implant

- FDA approved for 12 months
- Dosing
  - 50 mg implant
  - Supprelin (histrelin) diffuses at average rate of 65 ug/day
  - So, in theory, implant provides enough medication for 2 years!


Case Study: Addie

Clinical Presentation

- 8 year 2 month old female with history of breast development beginning around 7 years 10 months by report
- Recent 5 inch growth spurt in the past year
- Bone age at CA of 8 years 2 months is advanced to 12 years of age
- Tanner 3 breast on exam

Evaluation

- Laboratory evaluation consistent with central puberty.

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<thead>
<tr>
<th>Study</th>
<th>Results</th>
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<tbody>
<tr>
<td>LH</td>
<td>0.609 mIU/ml</td>
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<tr>
<td>FSH</td>
<td>2.4 mIU/ml</td>
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<tr>
<td>Estradiol</td>
<td>1.9 pg/ml</td>
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- Adrenal labs and thyroid labs also normal.
Case Study: Addie
Treatment

- Decision made to treat with GnRH agonist, Supprelin, for psychosocial reasons.
- Implant placed at 8 years 4 months of age.

15 months s/p implant
- Puberty exam stable
- Growth velocity prepubertal
- Bone age stayed stable after a year+ on treatment

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<tr>
<td>Baseline</td>
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<td>1.9</td>
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<td>7 weeks s/p implant</td>
<td>0.332</td>
<td>1.4</td>
</tr>
<tr>
<td>15 months s/p implant</td>
<td>0.088</td>
<td>1.3</td>
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What Would You Do?

- OPTION 1: Leave in longer
- OPTION 2: Remove and replace at 15 months
- OPTION 3: Remove and not replace
Case Study: Addie

Treatment

- Supprelin replaced at 9 years 10 months, after 16.5 months.
- 4 months later (21 months total on treatment) at 10 years 2 months she was suppressed.

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<td>4.5 months s/p 2nd implant (total supprelin 20.5 m)</td>
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- “The 50 mg histrelin-acetate implant provides sustained suppression for 12 months.”
- No statement that addresses this controversy.

A Single Histrelin Implant Is Effective for 2 years for Treatment of Central Precocious Puberty

- Prospective Study with 33 children with CPP
- Monitor at 6 month intervals
  - ICMA LH at 6 and 18 months
  - IF > 1 IU/L, then leuprolide stimulation test
  - Leuprolide stimulation test at 12 and 24 months
    - Suppression defined as LH <4 IU/L
  - Bone age at baseline, 12 months and 24 months

A Single Histrelin Implant Is Effective for 2 years for Treatment of Central Precocious Puberty (continued)

- Results
  - 29 patients completed the study
  - Peak LH at 12 and 24 months was equivalent
  - LH at 6 months and 18 months was pubertal for 17 and 14 patients, respectively
    - GnRH stimulation test confirmed complete HPG axis suppression in ALL cases!
  - Degree of skeletal maturation declined significantly over 24 months
  - Tanner staging improved or stabilized in vast majority of patients (2 did not finish study)
  - Difficulty with implant removal occurred in 12 cases (39%)
    - Implant breakage = 6 cases; Implant migration = 1 case; Need for perpendicular incision = 8


Experience with the Histrelin Implant in Pediatric Patients

- Review article
- Important advancement that histrelin implant is effective for 2 years based on 2013 study
- Safety
  - Implant breakage (22-39%) and difficulty with localization
  - Appear higher when left longer?


An Observation … Hmmm

- The Children’s Hospital of Philadelphia (unpublished data)
- Over 500 procedures
- Adverse events based on recall: 1 removed for mood changes, 1 for infection and several needed perpendicular incision for breakage
- Official chart review underway!
Advantages and Disadvantages with Longer Treatment

► Advantages
  • Less procedures, potentially less sedation
  • Reduce cost
  • Excellent HPG axis suppression

► Disadvantages
  • Difficulty monitoring suppression with an ICMA LH alone
        ▶ Many of patients ICMA LH does not revert back to prepubertal range despite suppression
        ▶ Disadvantage regardless of length of treatment
  • Surgical complications with implant removal

Should Addie Have Been Treated Longer With the Same Implant?

And One Dilemma Leads to Another….
Should We Use Routine Lab Monitoring for Children with Supprelin Implant?


- Tanner stage and growth monitored every 3-6 months
- BA monitored periodically
- NO consensus about the routine use of random or stimulated measurements of gonadotropins or sex steroids for monitoring therapy

LH monitoring for Supprelin Specifically

- Recall from study above by Lewis et al. looking at Supprelin for 2 years, LH was often NOT prepubertal, BUT a GnRH stim test confirmed suppression in ALL cases!
- Multiple studies show that random LH often remains pubertal in children treated with the Histrelin implant

One Dilemma Leads to Another…

….Should We Use Routine Lab Monitoring for Children with Supprelin Implant?

And I Leave You With That Dilemma to Ponder!
References


