Algorithmic clinical approach to children boy with delayed puberty

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QUESTIONS:

1. What is the definition of delayed puberty?

2. What can cause delayed puberty?

3. What is the appropriate evaluation of delayed puberty?

4. What is the typical presentation of constitutional delay of puberty?

5. How can we treat delayed puberty?
Delayed Puberty

- 3% of adolescents.
- Most are boys.
- Most will be found to have no pathology, and will have normal progression of puberty as soon as it starts.
- A variety of causes that can be diagnosed with proper evaluation.
Normal puberty in males begins between 9th and 14th year of their lifetime.

Approximately 97% of white boys have at least early signs of secondary sexual development by the age of 14 years.

Delayed puberty in boys is defined as a clinical condition in which the pubertal events start late, by the absence of testicular enlargement (testicular volume < 4 ml) beyond 14 years old.
Most delayed puberties in boys are functional (constitutional delay of growth and puberty, CDGP)

The study of Wehkalampi K and his coworkers on a large sample size demonstrated that approximately 65% of boys with delayed puberty had CDGP

It has a strong genetic basis and 50 to 75% of patients with CDGP have a family history of delayed puberty

Small proportion may have pathological causes of delayed puberty.
delayed puberty can be subdivided into:

- **Central**: The site of the problem lies in the hypothalamo–pituitary axis. Central delayed puberty includes syndromes of low gonadotropin production.

- **Peripheral**: The site of the problem lies in the gonads. Syndromes of primary gonadal dysfunction are associated with high gonadotropin production.
So etiologies of pubertal delay and pubertal failure include:

1. Normal or low serum gonadotropins production

2. Increased serum gonadotropins production
Normal or low serum gonadotropins production:

1. Constitutional delay of puberty and growth (CDGP): healthy patients with a clinical history of delayed growth and development with intact hypothalamo–pituitary axis
2. Central nervous system (CNS) disorders:

- Tumors,
- Head trauma,
- Brain radiation therapy,
- LHRH receptor mutation,
- Congenital adrenal hypoplasia (DAX1 mutation),
- Isolate gonadotropin deficiency,
- Isolated LH deficiency,
- Isolated FSH deficiency
3. General disease disturbing body maturation:

Secondary to chronic illness particularly:
Asthma,
Eczema,
cystic fibrosis and inflammatory bowel disease (IBD),
Oncological diseases
And endocrinopathies such as:
hypothyroidism,
hyperprolactinemia,
Cushing's disease and
diabetes mellitus,
functional hypogonadotropic hypogonadism is seen.
constitutional delayed puberty (CDGP)

- Such boys generally are healthy but short (below the 10th percentile and often well below the 3rd percentile),

- Penile length normal for a prepubertal boy (usually 6 to 7 cm stretched) and testes that measure 2.5 cm or less in length (or 4 mL in volume with a Prader orchiometer)

The natural history in boys who have CDGP is for the growth spurt to start sometime between the ages of 15 and 17 years

When puberty has not started by age 17 years, CDGP becomes less likely
Isolated gonadotropin deficiency (IGD) is a relatively rare congenital condition caused by complete or partial deficiency of GnRH, resulting in decreased or absent secretion of LH and FSH.

One clue to the diagnosis is that in many cases, affected boys have small penises (5 cm in length) due to low testosterone production during the prenatal period and the first 4 postnatal months. The testes often are small and difficult to palpate.

Another clue is that some boys who have this condition have Kallmann syndrome, in which IGD is accompanied by hyposmia or anosmia.
Increased serum gonadotropin production:

- Chromosomal alterations
- Primary testicular failure
- Anorchia
- Cytotoxic therapy
- Castration syndromes
- Genetic disorders
- Radiotherapy/chemotherapy
How can we distinguish between delayed puberty and other pathologic problems?

- The diagnosis is simple when elevated gonadotrophin levels indicate a primary gonadal lesion, or when the delayed puberty results from chronic illness.

- In contrast, when we have hypogonadotrophic hypogonadism, it is difficult to differentiate it from delayed puberty,
since low gonadotropin and low testosterone levels are found in both conditions and there is no known method that is wholly successful in differentiating between hypogonadotrophic hypogonadism and constitutional delayed puberty at an early stage.

For the same reason, a focused medical history, a directed physical examination, related laboratory tests, and medical imaging for correct diagnosis are needed.
Evaluation of Pubertal Delay

- **Careful History:**
  - Anosmia, galactorrhea, hypothyroidism
  - Excessive exercise
  - Chronic illness or psychiatric disease.
  - Family history.

- **Physical examination:**
  - Growth parameters.
  - Sexual maturity.
  - Stigmata of congenital syndromes.
Taking a history:

A detailed history is the first step in the diagnostic evaluation of a normal variant or an abnormal puberty. Taking a history from a child or parent will often show the cause of delayed puberty. Clinically appropriate questions and basic information include:
• Growth pattern up to the time of evaluation is very important.

• Boys with constitutional delay usually have delayed growth in childhood.

• They are shorter than patients with isolated gonadotropin deficiency that generally have normal height for age in the prepubertal period.
• Family patterns:

- A positive family history for pubertal delay would support the diagnosis of constitutional delay of puberty,

- A family history of **late development** may be present in up to 90% of cases.

- Their parents should be questioned about a history or symptoms of delayed growth spurt, voice breaking in the father and the pubertal milestones of siblings.

- Most of CDGP patient have a father (or sibling) who did not enter puberty until late (age 14 to 18 years).
• **Previous disease:**

Gastrointestinal disorders such as inflammatory bowel disease or celiac disease, as well as chronic renal failure, cardiac disease, asthma, and other severe chronic illnesses are causes of pubertal delay or may be associated with delayed puberty, especially when steroids have been used. In malnutrition and chronic diseases, weight loss to **below 80%** of ideal body weight can delay or arrest pubertal development.
• **History of gonadal dysfunction:**
  These include a previous history of cryptorchidism, orchidopexy, and gonadal irradiation.

• **Neurologic symptoms:**
  Symptoms of brain tumor include headache, visual disturbances, vomiting, and weakness of one or more limbs should be considered. Ability to smell like as toast burning or unpleasant odours such as rotten eggs that is seen in Kallmann's syndrome, should be asked.
History of psychiatric and behavioral abnormality:

Cognitive development or Behavioral abnormality in family is seen in Klinefelter's syndrome. Learning disability may be also a component of dysmorphic syndromes associated with delay puberty (e.g. Noonan’s syndrome).

Delayed cognitive development associated with obesity or dysmorphic features may suggest an underlying genetic syndrome that associated with gonadotrophins deficiency like as Prader-Willi syndrome.
Examination:
After the patient has answered all the questions, now it is time for the physician to help elicit further information about the symptoms through the following exams:

**General-examination** should always start with assessment of these index:

1. **Height- upper to lower segment ratio:**
   Children with constitutional delay are more likely to be short for age. Eunuchoidal body habitus is seen in Klinefelter's syndrome.

2. **Arm span**
   exceeds height by 5cm or more. This reflects the delayed closure of the epiphyses of long bones caused by hypogonadism.
• Weight:
Children who are underweight for height have an increased likelihood of having an underlying condition delaying HPG-axis activation like as malabsorption or underlying gastrointestinal disease.

Conversely, a relatively excess weight is a feature of growth hormone deficiency, hypothyroidism and glucocorticoid excess.
• Notice to axillary and pubic hair: Both **adrenarche** and **gonadarche** occur later than average in individuals with CDGP, whereas **adrenarche** usually occurs at a normal age in patients with isolated gonadotropin deficiency.

• General examination with particular attention to clubbing, blood pressure, and cardiac function, detection of cardiovascular abnormalities during systematic examination should alert the examiner to the possible diagnosis of **Noonan's syndrome**.
• Dysmorphic features:
  midline facial abnormalities (cleft palate), cryptorchidism,

• Examination of the genitalia and secondary sexual features:
  Ambiguous genitalia with undescending testes or inguinal hernia arouse suspicion of disorder of sex development (DSD).
• **Neurologic exam:**

  Evaluation of:
  • **visual defects** (including bilateral temporal field deficits), optic atrophy or **papilloedema**, and **red-green color blindness** are important. These abnormalities result from suprasellar extension of pituitary tumors

  • Test of sense of smell and anosmia;

    **Anosmia** is a variable feature of hypothalamic hypogonadism (**Kallmann's syndrome**). Because affected individuals often do not notice impaired testing with graded dilutions of pure scents is necessary

    **Congenital deafness** is associated with pure gonadal dysgenesis
Investigations:
After a complete evaluation and physical exam, Pediatrician is likely to do further testing:

- **Basal FSH and LH and serum testosterone are** the first step in the evaluation of male sexual function:
  - **High** gonadotropin levels represent hypergonadotropic hypogonadism such as primary testicular failure or Klinefelter syndrome
  - But single basal serum LH and FSH determinations are not useful to distinguish between constitutional delay and organic gonadotropin deficiency.

- Nevertheless, when serum gonadotropins are **normal** or **low**, constitutional delay of puberty is the most frequent diagnosis
Investigations

- Serum gonadotropin levels.
  - **High:**
    - Klinefelter.
    - Bilateral gonadal failure.
    - Need to Chromosomal analysis.
  
  - **Low or normal:**
    - Screen for occult chronic illness or endocrinopathy:
      - CBC, ESR.
      - Prolactin, TSH
    - IGD vs. constitutional delay.
    - Stimulation tests.
GnRH test:

- If basal gonadotropin levels are indefinite, it's may be helpful.
- At low levels, values obtained on ICMA are approximately 50% lower than those obtained on IFMA. **Values of <0.2** IU per liter on ICMA or <1.0 IU per liter on IFMA suggest IGD but are not diagnostic.

- In delayed puberty, a value above the **upper limit** of the normal range for the assay is a sensitive and specific marker of primary gonadal failure.
- So Endocrinologists sometimes measure LH and FSH after stimulation with GnRH Stimulated test.

- A predominant response of luteinizing hormone over follicle-stimulating hormone after stimulation or peak luteinizing hormone levels **of 5 to 8** IU per liter (depending on the assay) suggests the onset of central puberty.

- However, GnRH stimulation testing alone is not helpful in distinguishing between constitutional delay of puberty and hypogonadotropic hypogonadism,

- because both may show pre-pubertal patterns of gonadotropin secretion in response to stimulation
Measuring testosterone concentrations in boys after a 3-day series of human chorionic gonadotropin hormone (HCG) injections (which has LH-like actions on the testes) also has been used. Concentrations achieved in boys who have CDGP are higher than in those who have IGD, with overlap.

**Serum inhibin B:**
Prepubertal boys with a baseline inhibin B level of >35 pg per milliliter have a higher likelihood of CDGP. In boys, unmeasurable inhibin B indicates primary germinal failure.

**Serum prolactin:**
Elevated levels may indicate hypothalamic–pituitary tumors causing hypogonadotropic hypogonadism. In such cases, additional pituitary-hormone deficiencies may be present.
<table>
<thead>
<tr>
<th>Test</th>
<th>CDGP</th>
<th>HH</th>
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<tbody>
<tr>
<td>Testicular volume</td>
<td>&gt; 4 mL</td>
<td>&lt; 4 mL</td>
</tr>
<tr>
<td>Basal T</td>
<td>&gt; 1.7 nmol/L</td>
<td>&lt; 1.7 nmol/L</td>
</tr>
<tr>
<td>T response to hCG (1500 U EODIMX3)^[13]</td>
<td>&gt; 8 nmol/L</td>
<td>&lt; 3 nmol/L</td>
</tr>
<tr>
<td>LH after GnRH test (Nafarelin 0.1 mg/m^2)[^[14]</td>
<td>Increment &gt; 4.6 U/L</td>
<td>Increment &lt; 2 U/L</td>
</tr>
<tr>
<td>LH (3 h) after tripyorelin (0.1 mg/m^2)[^[12]</td>
<td>LH &gt; 14</td>
<td>LH &lt; 14</td>
</tr>
<tr>
<td>T after hCG × 3 days^[12]</td>
<td>T &gt; 9 nmol/L</td>
<td>T &lt; 9 nmol/L</td>
</tr>
<tr>
<td>LH (4 h) after decapeptyl (0.1 mg/m^2)[^[13]</td>
<td>LH &gt; 8 U/L</td>
<td>LH &lt; 8 U/L</td>
</tr>
<tr>
<td>T (7th day) after hCG × 3 (EOD)[^[13]</td>
<td>T &gt; 8 nmol/L</td>
<td>T &lt; 8 nmol/L</td>
</tr>
<tr>
<td>T after 24 h of IM low-dose hCG (15 U/kg. once)[^[15]</td>
<td>T &gt; 6 nmol/L</td>
<td>T &lt; 6 nmol/L</td>
</tr>
<tr>
<td>LH after low-dose GnRH (10 mcg IV)[^[16]</td>
<td>++ Response</td>
<td>No response</td>
</tr>
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CDGP: Constitutional delay of growth and puberty, HH: Hypogonadotropic hypogonadism. LH: Luteinizing hormone.
Neuroimaging:

Evaluate of tumors of the pituitary or hypothalamus; absent olfactory bulbs and tracts/ hypoplastic olfactory gyri (kallmann syndrome)

Bone Age:

A bone-age delay of >2 yr has arbitrarily been used as a criterion for CDGP but is nonspecific.
For psychological reasons, in boys of age 14 or older who show no signs of puberty, the most simple treatment is still a brief course of testosterone injections (testosterone enanthate, cypionate or cyclopropionate 50 mg sometimes up to 100 mg intramuscularly) every 4 weeks for 3-6 months.

Decades of experience confirm no effect on final height of such low dosage for short term.
If during the 3 to 6 months after discontinuing gonadal steroid therapy time the patient has not started to develop or grow at a normal rate and spontaneous puberty does not ensue or the concentrations of plasma gonadotropins and plasma testosterone do not increase, the treatment may be repeated.

Usually, only one or two courses of therapy are necessary. When treatment is discontinued after bone age has advanced, for example, to 13 to 14 years, patients with constitutional delay usually continue pubertal development on their own, whereas those with gonadotropin deficiency do not progress and may, in fact, regress.
Functional hypogonadotropin hypogonadism associated with chronic disease is treated by alleviating the underlying problem. Delayed puberty in this situation is usually a result of inadequate nutrition and low weight or excessive energy expenditure; when weight returns to normal values, puberty usually occurs spontaneously. Treatment with thyroxine will allow normal pubertal development in hypothyroid patients with delayed puberty.

Congenital or acquired gonadotropin deficiency as a result of a lesion or surgery requires replacement therapy with testosterone at an age approximating the normal age of onset of puberty.
References:


We Learn
10% of what we read
20% of what we hear
30% of what we see
50% of what we see and hear
70% of what we discuss
80% of what we experience
95% of what we teach others

William Glasser, MD, one of the fathers of modern psychology