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On behalf of Special Interest Group: Applied Genetics, it gives me immense pleasure and pride in presenting to you the fourth issue of newsletter “ReproGenQ” with the theme Puberty and Genetics. Puberty disorders are on the rise and it is vital to understand their pathophysiology especially the genetic aspects. Genomics may be the answer of many untold etiologies related to pubertal disorders. This issue pen down the overview of genetic regulation of puberty, approach to precocious and delayed puberty, genetics of inborn errors of metabolism and their effects on puberty. I hope this issue will give you an insightful reading.

Dr. Mona Sharma
Editor,
ReproGenQ
Approach To Precocious Puberty

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Approach to Delayed Puberty

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Genes regulating Puberty

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PHYSIOLOGY OF NORMAL PUBERTY

Normal pubertal onset requires a series of maturational steps and events which results in pulsatile secretion of gonadotropin-releasing hormone (GnRH) from hypothalamus and reactivation of hypothalamic-pituitary-gonadal (HPG) axis. The HPG axis remains functionally active during the fetal life from mid-gestation until term and then shortly after birth till 3-6 months of age which is also known as ‘mini-puberty’. Subsequently, HPG axis remains dormant till the onset of puberty. Reactivation of HPG axis is controlled by various genetic, neuroendocrine, environmental and metabolic factors.

The physical and psychosocial changes during puberty are a result of gonadarche and adrenarche. Gonadarche is increased secretion of gonadal steroids (testosterone from testes or estrogen from ovaries) and is often preceded by adrenarche by 2-3 years, however the two are independent of each other. Gonadarche is initiated by pulsatile secretion of GnRH from hypothalamus and manifests as thelarche or breast development (transition from B1 to B2) in girls and testicular enlargement (transition from G1 to G2) in boys (Table 1 and 2). Adrenarche refers to increased production of adrenal androgen from adrenal zona reticularis. It is independent of adrenocorticotropic hormone (ACTH) secretion and is characterized by development of axillary and pubic hair, body odor, skin oiliness and mild acne.

DISORDERS OF PUBERTY

Over the past few decades, a secular trend toward the earlier age of onset of normal puberty has been demonstrated. The average age of onset of menarche has been found to be decreased from 17 years in early nineteenth century to 13 years in the mid-twentieth century. Pubertal disorders can be divided into precocious puberty and delayed puberty. When the age of onset of puberty is below or above 2.5 SD of the mean age of puberty in general population, it is defined as abnormal puberty. Precocious puberty (PP) is defined as appearance of secondary sexual characteristics before the age of 8 years in girls and 9 years in boys. Precocious puberty is more common in girls than boys.

PREOCIOUS PUBERTY

Precocious puberty can be classified into 3 categories depending upon the underlying etiopathogenesis, source of hormone production and progression of puberty.

1. Incomplete forms of precocious puberty: This includes isolated forms of premature thelarche, pubarche and menarche. They usually regress with time and might or might not be due to underlying hormonal imbalance.

2. Central precocious puberty (CPP): Also known as true precocious puberty or gonadotropin-dependent precocious puberty. This is mainly caused due to early maturation of HPG axis and is always isosexual. The etiologies of CPP are mainly similar in girls and boys. However, approximately 90% of girls usually have idiopathic CPP, boys are much more likely to have an identifiable pathology.

3. Peripheral precocious puberty: Also known as pseudo-precocious puberty or gonadotropin-independent precocious puberty. This is mainly caused due to excessive secretion of gonadal sex hormones or adrenal androgens independent of GnRH and may be isosexual or heterosexual.

4. Combined central and peripheral precocious puberty: Also known as mixed type of precocious puberty. These cases usually have peripheral precocious puberty to begin with, but as the bone age advances, it leads

INTRODUCTION

Puberty is a period of transition from childhood to adulthood which is characterized by accelerated linear growth, behavioural changes, psychosocial and sexual maturation. Abnormal onset and progression of puberty can result from a range of benign and pathological etiologies and can affect physical and psychosocial well-being of a child. An astute physician should be able to differentiate pathological causes from normal variants of pubertal development and treat accordingly.
to activation of HPG axis leading to central precocious puberty.

Etiology and differential diagnosis of precocious puberty

Various etiologies and differential diagnosis of different forms of precocious puberty has been enlisted in Table 3 and 4.

INCOMPLETE FORMS OF PRECOCIOUS PUBERTY

Premature adrenarche/pubarche

Premature adrenarche or pubarche is defined as a form of incomplete precocious puberty which is characterized by the presence of pubic hair, axillary hair, adult type body odor, oily skin and acne before the age of 8 years in girls and 9 years in boys. The characteristic feature is bone age will be similar to or only slightly accelerated to chronological age; and basal and post GnRH stimulation levels of luteinizing hormone (LH) and follicle stimulating hormone (FSH) will be prepubertal. The exact etiopathogenesis of premature adrenarche has not been elucidated; possible explanation could be precocious maturation of zona reticularis of adrenal gland leading to increase in the levels of adrenal androgens in the blood or increase in the activity of androgen receptors leading to hypersensitivity of hair follicles to circulating levels of sex steroids or androgens. Various studies have found association of premature adrenarche with low birth weight, hyperinsulinism, metabolic syndrome, polycystic ovary syndrome (PCOS) and hyperandrogenism during adolescence. The diagnosis of premature adrenarche is mainly based on exclusion of common causes including precocious puberty, non-classic congenital adrenal hyperplasia (CAH) and virilizing adrenal tumors. Laboratory evaluation may be needed to exclude pathological causes including serum dehydroepiandrosterone (DHEA), dehydroepiandrosterone sulfate (DHEAS), androstenedione, 17-OH-progesterone levels (both basal and post ACTH stimulation test), basal and post GnRH stimulation LH and FSH levels and x ray wrist to look for bone age. Treatment depends upon underlying etiology and is mainly supportive including weight management, lifestyle modification and close surveillance over 3-6 months to look for progression of puberty.

PREMATURE THELARCHE

Premature thelarche is isolated unilateral or bilateral breast development before the age of 8 years in girls without appearance of other secondary sexual characteristics. The classical feature that distinguishes it from precocious puberty is that bone age correlates with the chronological age; and basal and post GnRH stimulated LH levels will be in the prepubertal range. The possible explanations for premature thelarche include obesity, excessive exposure to exogenous estrogens, increased sensitivity of breast tissue to circulating levels of estrogen and isolated increase in FSH secretion. Few authors have found association of premature thelarche with increased ovarian follicular development without increase in the size of uterus. Treatment involves supportive management and counselling of parents as it spontaneously regresses with age. Earlier the age of development of thelarche, the more chances that it will regress spontaneously.

PREMATURE MENARCHE

Premature menarche is defined as menstrual cycle like vaginal bleeding before the age of 9 years in girls without appearance of other secondary sexual characteristics. It is rare and may appear just once or may be recurring. It usually resolves over next 1-2 years. The exact etiopathogenesis is still unknown, hypersensitivity of endometrium to low levels of circulating estrogen is the proposed mechanism. Ultrasound examination reveals prepubertal size of uterus and endometrial maturation. The main purpose of evaluation is to exclude other causes of uterine bleeding including trauma, foreign body, sexual abuse, genital tract infections or tumors, ovarian cysts and central precocious puberty.

CONSEQUENCES OF PRECOCIOUS PUBERTY

Precocious puberty has several adverse outcomes on psychological and physical health of a child and needs thorough evaluation and treatment. Sustained increase in circulating sex steroid levels specially estradiol results in early fusion of epiphysis, resulting in shorter final adult height. High circulating sex steroid levels leads to psychological and emotional disturbances. Early menarche has also been found to be associated with metabolic syndrome including obesity, hypertension, insulin resistance and type 2 diabetes mellitus and increased risk of cardiovascular diseases including stroke and ischemic heart disease. Few studies have found increased risk of breast cancer in girls with CPP.

EVALUATION OF PRECOCIOUS PUBERTY

A step wise approach is needed to make appropriate diagnosis and avoid unnecessary treatment as suggested in figure 1.

HISTORY AND PHYSICAL EXAMINATION

The physician should take a thorough clinical history including family, past medical and surgical history. Age of onset of secondary sexual characteristics, growth spurt, nutritional intake, history of intake of chemotherapy, radiotherapy, use of exogenous sex steroids, chronic application of ointment containing sex steroids should be thoroughly evaluated. History of headache, vision abnormality or neurological deficit may point towards underlying intracranial pathalogy. History of early puberty in the family members should also be sought which might indicate genetic etiology.

The physical examination includes careful assessment of pubertal staging as suggested in Table 1 and 2. Genital organ assessment is the most important step in making diagnosis of precocious puberty. Isolated presence of single secondary sexual characteristics may indicate incomplete forms of precocious puberty. In boys, testicular volume should be measured using orchidometer and length using caliper. In girls, breast buds should be carefully inspected and palpated for glandular tissue to distinguish between lipomastia seen in obesity and thelarche seen in precocious puberty. Height, weight, body mass index (BMI) should be appropriately measured and plotted over growth charts. Target height should be calculated using the formula: (mother height + father height + 13 cms in boys or - 13 cms in girls)/2 and should be plotted on growth charts. Children with PP may appear to have tall stature initially but will later have short stature due to early epiphyseal fusion. Bayley-Pinneau method may also be used to predict adult height using bone age. A thorough head to toe examination should be done including neurological assessment, fundoscopic examination or skin abnormalities which may point towards underlying etiology as mentioned in table 5.

LABORATORY EVALUATION

Hormonal assessment should be planned according to the differential diagnosis based on history and examination. Initial work up should include measurement of basal LH, FSH, estrogen in girls and testosterone in boys and bone age assessment. At the onset of puberty, sex steroids begin to rise and estradiol levels > 100pg/ml and testosterone > 30 ng/dl are seen in girls and boys, respectively. Bone
age should be assessed using x-rays of small bones of hand and wrist and compared using Greulich and Pyle’s atlas. Bone age advancement by more than 2.0 SD is suggestive of precocious puberty. Basal and stimulated gonadotrophins (LH and FSH) and sex steroids are indicators in cases of CPP. Basal LH, measured in the morning, is the most sensitive marker for the diagnosis of precocious puberty and can be measured by various assays including immunofluorometric (IFMA), immunochemiluminiscence (ICMA), and electrochemiluminiscence (ECL). Basal LH values > 0.3 IU/L (ICMA, ECL) or > 0.6 IU/L (IFMA) are suggestive of activation of HPG axis and point towards central precocious puberty. Low basal LH levels do not rule out the diagnosis and GnRH stimulation test should be done to confirm the diagnosis of CPP and differentiate it from peripheral PP. A predominant LH response with stimulated LH levels >5-6 IU/L are considered pubertal whereas predominant FSH response is common in isolated thelarche. Isolated increment of estrogen or testosterone with bone age advancement along with prepubertal levels of LH may be suggestive of peripheral precocious puberty.

In cases of suspected peripheral precocious puberty, adrenal steroids including 17-OH-progesterone, DHEA, DHEAS and cortisol should be measured. ACTH stimulation may be required in certain cases to rule out non classic CAH.

IMAGING

Brain imaging including MRI brain (specifically pituitary and hypothalamic region) may be done to look for structural abnormalities. MRI brain should be done in almost all boys aged less than 9 years and girls aged less than 6 years with features of central precocious puberty. Requirement of MRI brain in girls aged 6-8 years with feature of CPP is debatable. However, neuroimaging is required in all children with neuroendocrine abnormality and rapidly progressive pubertal signs. Pelvic and gonadal ultrasonography (USG) is performed in girls to see the size and morphology of ovaries and uterus with endometrial thickness. Uterine length of less than 4.0 cm and thickness less than 1 cm is typically seen in prepubertal girls. USG may also reveal gonadal tumor or malignancy, if present in certain cases. In cases of boys, USG may be done to look for testicular enlargement, measurement of length and volume and to look for asymmetry or malignancy. USG/ CT adrenals is done in cases of suspected peripheral PP to look for adrenal size and adrenocortical tumors.

TREATMENT

Precocious puberty

The mainstay of treatment of CPP remains GnRH agonists. It has been found that sustained high concentration of GnRH results in downregulation and suppression of HPG axis. Different formulations of GnRH agonists are available including monthly (3.75 mg/7.5 mg) or 3 monthly (11.25 mg/22.5 mg/30 mg) IM depot injections of leuprolide acetate, monthly depot injection being the most commonly used regimen. Recent studies have found 3- monthly depot injections of leuprolide acetate at 11.25mg and 30 mg doses to be equally safe and effective for long term use and have also been approved by FDA. Adverse reactions include local reaction, pain at injection site and rarely abscess formation.

Peripheral precocious puberty

Treatment of children with peripheral PP depends upon the underlying etiology. Major treatment modalities include androgen receptor blockers including spironolactone or bicalutamide; aromatase inhibitors including anastrozole or letrozole and estrogen receptor blockers including fulvestrant to decrease the effect of excessive androgen production and retard the skeletal maturation.

Outcomes of treatment

The primary goal of treatment of CPP is preservation of final adult height. Studies evaluating the effect of treatment vs no treatment of CPP on final adult height are limited. Slowly progressive or non-progressive forms of CPP may not affect final adult height and may not need any treatment. Some authors suggest a period of observation for 3-6 months to look for progression of puberty prior to starting any treatment. The effect of treatment on final adult height depends upon multiple factors including age of onset of puberty, age of initiation of treatment, skeletal maturation and pubertal staging. Maximum effect of treatment has been found in girls with onset of puberty before 6 years of age, while the effect is variable in girls aged 6-8 years. No effect on final adult height has been found when treatment is initiated after 8 years of age.

Many studies have evaluated the long-term effects of GnRH agonists on reproductive functions in children with central precocious puberty. They found no difference in the incidence of menstrual irregularity, dysmenorrhea, number of pregnancies, abortions and pregnancy outcomes as compared to the general population. The effect of CPP and treatment with GnRH agonists on PCOS and BMI is variable. Few authors have found increased incidence of PCOS in children with CPP with or without treatment with GnRH agonist while other have found little or no difference. Higher BMI has been noted in girls with CPP as compared to the general population, probably due to the effect of puberty on BMI. However, no adverse effect of treatment with GnRH agonist has been found on BMI. Bone mineral density has been found to decrease transiently during treatment with GnRH agonists, probably due to suppression of ovarian function, but is regained after discontinuation of treatment. Studies evaluating the psychological effects of treatment with GnRH agonists are limited with variable results and needs further evaluation.

Monitoring

Children receiving treatment with GnRH agonists should be monitored by clinical and laboratory parameters. Clinical evaluation includes regression of secondary sexual characteristics, decrease in height velocity and increase in final predicted adult height. Bone age should be monitored 6-12 monthly. Measurement of LH levels monthly or 3 monthly after receiving GnRH agonists is the test of choice, levels below 4 IU/L suggests adequate suppression of HPG axis.

Discontinuation of treatment

No standardized age for discontinuation of therapy has been finalized till date. Most people individualize the duration of treatment based on chronological age, absolute and predicted adult height, psychological factors and family preference. However, maximum benefit in terms of optimal height gain has been found when treatment is stopped at a bone age of 12 years in girls and 13 years in boys.

Resumption of HPG axis after treatment discontinuation

Average time to menarche after discontinuation of GnRH agonists depot injections has been found to be 1.5±/- 0.5 years. Slightly shorter time to menses has been found in girls who have experienced menarche before the start of treatment. Although data in boys is less, advancement in Tanner staging has been found within 6 months of discontinuation of treatment.
CONCLUSION

Normal progression of puberty is a multifactorial process. Disorders of puberty can affect physical and psychological well being of a child. It is important to distinguish pathological pubertal development from normal variants of puberty to avoid unnecessary investigations and treatment. The decision to treat precocious puberty is mainly based on clinical, laboratory parameters and bone age advancement. Timely initiation of GnRH analogues helps in preventing the progression of precocious puberty and comorbidities associated with it.

Table 1: Sexual maturity rating in girls

<table>
<thead>
<tr>
<th>SMR stage</th>
<th>Breast development (B)</th>
<th>Pubic hair</th>
<th>Pubertal event</th>
<th>Mean age of onset (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prepubertal (B1)</td>
<td>None</td>
<td>None</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Subareolar breast bud (B2)</td>
<td>Sparse, long, slightly pigmented, along the medial labia</td>
<td>Peak HV (mean: 8.3 cms/year)</td>
<td>10 (8-12) years</td>
</tr>
<tr>
<td>3</td>
<td>Breast and areola enlarge further to form a continuous rounded contour (B3)</td>
<td>Darker, coarser, more curled, spread sparsely over the mons pubis</td>
<td>Peak HV</td>
<td>-</td>
</tr>
<tr>
<td>4</td>
<td>Areola and nipple form a secondary mound above the breast contour (B4)</td>
<td>Adult type, no extension to medial thighs</td>
<td>Menarche</td>
<td>12.5 (9-15) years</td>
</tr>
<tr>
<td>5</td>
<td>Nipple projection without the secondary mound, Mature adult stage (B5)</td>
<td>Adult type, extending to medial thighs</td>
<td>Menarche</td>
<td>-</td>
</tr>
</tbody>
</table>

HV: Height velocity

Table 2: Sexual maturity rating in boys

<table>
<thead>
<tr>
<th>SMR stage</th>
<th>Genital development (G)</th>
<th>Pubic hair</th>
<th>Pubertal event</th>
<th>Mean age of onset (Range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Prepubertal, TV &lt; 3ml (G1)</td>
<td>None</td>
<td>None</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Increase in TV (≥4ml) and length (≥2.5 cms), enlargement and change in texture of scrotum (G2)</td>
<td>Sparse, slightly pigmented, mainly at the base of penis</td>
<td>None</td>
<td>11.5 (9.5-14) years</td>
</tr>
<tr>
<td>3</td>
<td>TV ≥10 ml, testicular length ≥3.6 cms (G3)</td>
<td>Darker, coarser, more curled, spread sparsely over the pubis</td>
<td>Peak HV (mean: 9.5 cms/year), spermarche</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>TV ≥15ml, testicular length ≥4.1 cms (G4)</td>
<td>Adult type, no extension to medial thigh</td>
<td>Peak HV, spermarche</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>TV ≥20 ml, testicular length ≥4.5cms (G5)</td>
<td>Adult type, extension to medial thigh</td>
<td>None</td>
<td></td>
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</tbody>
</table>

TV: Testicular volume; HV: Height velocity
<table>
<thead>
<tr>
<th>Category</th>
<th>Differential diagnosis</th>
</tr>
</thead>
</table>
| Central precocious puberty (Male and females) | • **Idiopathic**  
• **Genetic**  
  i. Gain of function mutation in *KISS1* and *KISS1R* gene  
  ii. Loss of function mutation in *MKRN3* (familial CPP)  
  iii. Loss of function mutation in *DLK1* gene  
  iv. Chromosomal abnormalities  
• **CNS abnormalities**  
  i. Hypothalamic hamartomas  
  ii. CNS tumors: Astrocytoma, ependymoma, optic glioma, pinealoma, neurofibroma, craniopharyngioma  
  iii. Congenital CNS malformations: Suprasellar or arachnoid cysts, septo-optic dysplasia, hydrocephalus, meningomyelocele, spina bifida, vascular malformations.  
  iv. Acquired CNS lesions: Brain abscess, meningitis, encephalitis, sarcoidosis, tuberculosis, radiation, trauma  
• ** Syndromic causes**  
  i. Neurofibromatosis type 1, Tuberous sclerosis, Sturge weber syndrome, Cowden syndrome, Russell-Silver syndrome  
• ** Environmental factors**  
  i. International adoption  
  ii. Early life social stressor  
  iii. Nutritional excess or deprivation  
  iv. Prepubertal exposure to sex steroids  

*KISS1*: Kisspeptin 1; *MKRN3*: Makorin ring finger protein 3; *DLK1*: Delta Like Non-Canonical Notch Ligand 1; *CNS*: Central nervous system
<table>
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<th>SMR stage</th>
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<th>Pubertal event</th>
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<td>2</td>
<td>Increase in TV (≥4ml) and length (≥2.5 cms), enlargement and change in texture of scrotum (G2)</td>
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</tr>
<tr>
<td>3</td>
<td>TV ≥10 ml, testicular length ≥3.6 cms (G3)</td>
<td>Darker, coarser, more curled, spread sparsely over the pubis</td>
<td>Peak HV (mean: 9.5 cms/year), spermarche</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>TV ≥15ml, testicular length ≥4.1 cms (G4)</td>
<td>Adult type, no extension to medial thigh</td>
<td>Peak HV, spermarche</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>TV ≥20 ml, testicular length ≥4.5 cms (G5)</td>
<td>Adult type, extension to medial thigh</td>
<td>None</td>
<td></td>
</tr>
</tbody>
</table>

TV: Testicular volume; HV: Height velocity
Breast development (B2) < 8 years in girls and 
Testicular enlargement to >4ml (G2) at < 9 years in boys

Detailed history, examination and appropriate laboratory investigations 
(Basal and post GnRH LH and FSH levels, serum estrodiol (girls)/
testosterone (boys), thyroid function tests, x ray wrist for bone age)

Advanced bone age or accelerated growth velocity

No
Isolated examination findings
Isolated breast
enlargement
Premature
Thelarche
Isolated vaginal
bleeding
Premature
Menarche

Yes
Measure basal and post GnRH LH

Prepubertal
LH levels
Peripheral
PP
Evaluate and treat accordingly
Normal
Premature adrenarche
Follow up for 3-6 months and
watch for progression

Elevated
Consider CAH, adrenal tumors
Cushing syndrome
Evaluate and treat accordingly

Pubertal
LH levels
Central
PP
Brain MRI
Normal
Lesion present

GnRH: Gonadotropin releasing hormone; LH: Luteinizing hormone; FSH: Follicle stimulating hormone; DHEA: Dehydroepiandrosterone; DHEAS: Dehydroepiandrosterone sulfate; PP: Precocious puberty; CAH: Congenital adrenal hyperplasia; CNS: Central nervous system; MRI: Magnetic resonance imaging
### Table 5: Clinical clues to etiology of precocious puberty

<table>
<thead>
<tr>
<th>Clinical findings</th>
<th>Possible etiology</th>
</tr>
</thead>
<tbody>
<tr>
<td>Café au lait spots</td>
<td>McCune-Albright syndrome</td>
</tr>
<tr>
<td>Axillary freckling/ neurofibromas/ optic glioma/ Lisch nodules</td>
<td>Neurofibromatosis</td>
</tr>
<tr>
<td>Ash leaf macule/ angiofibromas/ shagreen patch/ periungual fibroma</td>
<td>Tuberous sclerosis</td>
</tr>
<tr>
<td>Short stubby hands/ Obesity/ Behavioural abnormalities</td>
<td>Prader-Willi syndrome</td>
</tr>
<tr>
<td>Increased body mass index</td>
<td>Obesity</td>
</tr>
<tr>
<td>Abdominal pain or mass</td>
<td>Gonadal malignancy</td>
</tr>
<tr>
<td>Asymmetric testes</td>
<td>Gonadal tumor</td>
</tr>
<tr>
<td>Reddened or pinkish vaginal mucosa</td>
<td>Exogenous estrogen exposure</td>
</tr>
<tr>
<td>Thyromegaly</td>
<td>Hypo or hyperthyroidism</td>
</tr>
<tr>
<td>History of head trauma/ headache/ vision abnormality/ abnormal neurological examination</td>
<td>Intracranial pathology leading to central precocious puberty</td>
</tr>
<tr>
<td>Family history of precocious puberty</td>
<td>Genetic cause</td>
</tr>
<tr>
<td>Dysmorphism</td>
<td>Syndromic causes</td>
</tr>
</tbody>
</table>

GnRH: Gonadotropin releasing hormone; LH: Luteinizing hormone; FSH: Follicle stimulating hormone; DHEA: Dehydroepiandrosterone; DHEAS: Dehydroepiandrosterone sulfate; PP: Precocious puberty; CAH: Congenital adrenal hyperplasia; CNS: Central nervous system; MRI: Magnetic resonance imaging

**REFERENCES**

Puberty is the transitional phase from childhood to adolescence. It is characterised by a series of neuroendocrinial mechanisms which leads to physical growth (growth spurt) and further development of reproductive system. Onset of puberty requires a functional hypothalamic-pituitary-gonadal axis and conditions which affects this axis also affects the onset of puberty. Tanner’s Staging is the most widely used tool to assess the progression of pubertal development.

\[
\text{Hypothalamus} \quad \text{GnRH release} \quad \text{Pituitary} \quad \text{Gonadotropins (LH & FSH)}
\]

Ovaries - estrogen and menstrual cycle
Testes - testosterone and sperm production

**Definition:**

Delayed puberty is defined as delay in onset of puberty by 2 or more standard deviation later than the mean age of onset in a given population. In general, it is failure of breast development by the age of 13 years in girls, and absence of signs of testicular development (≤4 ml) by the age of 14 years or failure of completion of testicular development by 17 years of age in boys.

It is different from Primary amenorrhea which is defined as the absence of menses by 15 years of age or absence of menses 3 years after initiation of breast development.

---

**ETIOLOGY:**

**Table 1:**

<table>
<thead>
<tr>
<th>Constitutional (Most common)</th>
<th>Autosomal dominant inheritance, Short stature, Delayed skeletal maturation</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Familial – delayed onset of puberty in parents/family members</td>
</tr>
<tr>
<td></td>
<td>Idiopathic</td>
</tr>
<tr>
<td>Low body fat</td>
<td>Anorexia</td>
</tr>
<tr>
<td></td>
<td>Athletes</td>
</tr>
<tr>
<td>Chronic illness</td>
<td>IBD - Chron’s</td>
</tr>
<tr>
<td></td>
<td>Chronic Renal Failure</td>
</tr>
<tr>
<td></td>
<td>Coeliac disease</td>
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<tr>
<td></td>
<td>Cystic fibrosis</td>
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<td></td>
<td>Haemochromatosis</td>
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<tr>
<td>Hypogonadism</td>
<td>Hypergonadotropic</td>
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<td></td>
<td>Primary Ovarian insufficiency (Turner)</td>
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<td></td>
<td>Chemotherapy</td>
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<td></td>
<td>Autoimmune</td>
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<tr>
<td></td>
<td>Hypogonadotropic</td>
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<tr>
<td></td>
<td>Hypothalamic (Kallman syndrome)</td>
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<td></td>
<td>Pituitary</td>
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</tbody>
</table>

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**APPROACH TO DELAYED PUBERTY**

**Dr Antima Rathore**

M.S. (OBG), Registrar, Nottingham University hospitals
NHS trust, Nottingham

**Correspondence:** dr_antima@hotmail.com
<table>
<thead>
<tr>
<th>Genetic</th>
<th>Pure gonadal dysgenesis (46,XX or 46,XY)</th>
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<tbody>
<tr>
<td></td>
<td>Klinefelter’s syndrome</td>
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<td></td>
<td>Turner syndrome</td>
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<td></td>
<td>Prader-Willi syndrome</td>
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<td>Hormonal</td>
<td>Hyperprolactinaemia</td>
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<td></td>
<td>Hypothroidism</td>
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<td></td>
<td>Growth hormone deficiency</td>
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<tr>
<td>Environmental</td>
<td>Chemical exposure</td>
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<tr>
<td>Psychological</td>
<td>Stress</td>
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<td></td>
<td>Social deprivation</td>
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<td>Steroid Therapy</td>
<td>Asthma</td>
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<td></td>
<td>Nephrotic syndrome</td>
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<tr>
<td>Other</td>
<td>Androgen insensitivity</td>
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<td></td>
<td>Bilateral cryptorchidism/orchidopexy</td>
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<td></td>
<td>Trauma/torsion</td>
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<td></td>
<td>Irradiation – gonadal/HP axis</td>
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<td></td>
<td>Craniopharyngioma</td>
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<td></td>
<td>Chemotherapy</td>
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<td></td>
<td>Optic glioma</td>
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<td>Post-surgery</td>
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</tbody>
</table>

d. Features/history suggestive of Kallmann’s, cystic fibrosis, Turner syndrome, asthma, childhood malignancy etc.

**EXAMINATION:**

1. Auxology - Measure weight, height and body mass index using reference charts and interpret using parenteral ranges as reference. Look for the growth pattern and for that serial monitoring for 2-3 years may be helpful. Long-standing (borderline) short stature followed by pubertal delay suggests constitutional delay
2. Nutritional status - eating disorders and chronic disease
3. Vital signs - hypothermia, bradycardia, hypertension
4. Pubertal staging - must be done using Tanner’s staging
5. Arm span exceeding the height by more than 5 cm points towards hypogonadism. It is because of delayed epiphyseal closure owing to lack of sex steroids.
6. Physical Examination
   a. Examination of the introitus, hymen, and clitoris - identify disorders of sex development.
   b. Testicular volume using Prader’s Orchidometer
   c. Features suggestive of hypogonadism - micropenis, cryptorchidism, midline defects
   d. Features/history suggestive of Kallmann’s, cystic fibrosis, Turner syndrome, asthma, childhood malignancy etc.
7. Systemic examination – Cardiovascular system, Ocular examination (tumor or congenital abnormalities)

**INVESTIGATIONS:**

A clinical diagnosis is made based on the history and examination and investigations are individualised. Cases of constitutional delay does not require any investigation except determining bone age and prediction of final height. Evaluation on gonadal axis is done only in very selected cases.

1) Chronic disease panel
2) Hormonal assays
   a. LH
   b. FSH
   c. Estradiol (in girls)
   d. Testosterone (in boys)
   e. Others – TSH, Prolactin, Cortisol
3) X-ray left wrist - to determine the bone age
Table: 2

<table>
<thead>
<tr>
<th>LH</th>
<th>FSH</th>
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<tbody>
<tr>
<td>↑</td>
<td>Primary hypogonadism (cause is at gonadal level)</td>
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<tr>
<td>↓</td>
<td>Constitutional delay</td>
</tr>
<tr>
<td>↓ or normal LH &amp; FSH</td>
<td>Hypothalamic-pituitary disorders</td>
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<tr>
<td></td>
<td>Hypothyroidism</td>
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<td></td>
<td>Hyperprolactinaemia</td>
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</tbody>
</table>

4) Genetic testing – Karyotype
5) Routine tests – Complete blood count, ferritin, LFT, KFT, electrolytes, urinalysis, and culture
6) MRI brain – hyperprolactinaemia, tumour
7) Ultrasound pelvis in girls

TREATMENT:

Counselling - It is vital to explain the cause, possible treatment, and their benefits. Provide psychological support where needed.

Main aim of medical treatment in cases of delayed puberty are -
1) Growth optimisation
2) stimulating secondary sexual characteristics,
3) Treatment of underlying cause. Once the process of puberty starts, it accelerates on its own. Care must be taken that the changes induced should be gradual to allow the adjustment.

CONSTITUTIONAL DELAY

Girls- In cases with constitutional delay, breast development will start eventually. However, estrogen supplements can be given for these cases, specially if it has psychological impact.

Oral low dose ethinyl oestradiol (estrogen) for six months to a year. Estrogen stimulates the breast development. Once the natural puberty takes over the breast development will continue and at this time estrogen supplementation can be withdrawn.

Boys- If there is a strong family history and no other causes of delay of puberty, boys less than 16 years can be observed for natural puberty to catch up.

a) Anabolic steroids may induce the growth in boys with constitutional delay who are mainly concerned with growth delay alone. They will not stimulate the secondary sexual characteristics.

Oxandrolone one/half tablet, once a day for three to four months.

b) Testosterone - can induce the development of secondary sexual characteristics as well as the associated growth spurt. Treatment should be continued for 3 months. Growth spurt will continue even after stopping the treatment.

Different routes of testosterone administration are as follow-

i) Long-acting intramuscular injection - given monthly for three to four months.
ii) Oral testosterone - Oral supplements can be used but the absorption is unreliable.

It is important to note that the final height achieved is not affected by either anabolic steroids or testosterone. They only affect the rate of growth. Treatment with Growth hormone or gonadotropins offer no additional benefits as testosterone and estrogen will stimulate the production of growth hormones, and cases of constitutional delay do not have defect in Hypothalamo-pituitary-gonadal axis.

Low body fat: Promote adequate nutrition uptake and healthy lifestyle.

Primary Hypogonadism:
Girls - They will need lifelong low dose estrogen supplement in form of hormone replacement therapy (HRT). As it is well known that estrogen is required for sexual development as well as general well-being. Modes for HRT- estrogen tablets or patches (increasingly used). Oral contraceptive pills can be used once puberty has been established.

Start with low dose and increase the dose every 6 months. Caution should be taken as early administration of high dose of estrogen may cause early epiphyseal closure resulting in short stature. Add progesterin at the age of 13 to start the periods. Estrogen priming is important before adding progesterone to get withdrawal bleed. Also, estrogen promotes breast development whereas progesterone may have adverse effect on breast development. For this reason, OCP should not be used to induce puberty.

<table>
<thead>
<tr>
<th>Age</th>
<th>Ethinyl-oestradiol (mcg)</th>
<th>Oral Oestradiol (mcg/kg)</th>
<th>Oestradiol patch (mcg/24 hr)</th>
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</thead>
<tbody>
<tr>
<td>12</td>
<td>10</td>
<td>5.0</td>
<td>3.1-6.25</td>
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<tr>
<td>13</td>
<td>15</td>
<td>7.5</td>
<td>6.25-12.5</td>
</tr>
<tr>
<td>14</td>
<td>20</td>
<td>10.0</td>
<td>12.5-18.8</td>
</tr>
</tbody>
</table>

Progesterone – Although Norethisterone is a potent progestogen, but it is not given in these cases and considered excessive. Whereas Medroxyprogesterone acetate or Micronized progesterone are the preferred preparations. They can be added for 12-14 days in every cycle or once every 2-3 months to reduce the number of withdrawals bleeding a year. Oral contraceptive pill may also be used to provide the progesterone supplementation.

Boys - They will require life-long testosterone supplement for normal sexual growth and function. After puberty is attained, gonadotropin injections/pump can be used for testicular growth and sperm production. Various routes for testosterone administration - Intramuscular injections every 1-3 months, Implants changed every 3-6 months (uncommon), daily oral capsules, transdermal patches or gel applied daily, gum or buccal testosterone.
Figure: 1 Management of Delayed Puberty

1. Underweight
   - Eating disorders
   - Athlete
   - Treatment
     - Diet & lifestyle modification

2. Not underweight
   - Evidence of chronic systemic disease/endocrinological or metabolic disorder
     - Evaluate accordingly

3. ↑FSH ↑LH
   - Prepubertal/pubertal bone age
   - Prolactin – normal
     - Karyotype
       - Normal
       - Primary Gonadal Dysgenesis
       - Abnormal
       - POI
       - Gonadotropin bioactivity/resistance
       - Steroidogenic block

4. Low FSH/LH/E2/Testosterone
   - Prepubertal bone age
   - Prolactin – normal
   - Constitutional
   - Hypogonadotropic hypogonadism

5. Low FSH/LH/E2/Testosterone
   - Prepubertal bone age
   - Prolactin – High
   - Brain MRI
     - Abnormal
     - - Prolactinoma
     - - Pituitary stalk compression
     - Normal
     - - Medication
     - - Renal failure
     - - Idiopathic

REFERENCES:


GENETICS OF INBORN ERRORS OF METABOLISM AND THEIR IMPACT ON PUBERTY

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ABSTRACT

Inborn errors of metabolism (IEMs) are rare genetic disorders resulting from an enzyme defect in biochemical and metabolic pathways which affects proteins, fats, carbohydrates metabolism leading to impaired organ function. These disorders can have a wide variety of multisystemic presentations, several of which overlap with more common disorders of adolescence. They have complex pathophysiology, biochemical workup, and molecular analysis, and complicated therapeutic management. Historically, thought of as pediatric disorders, inborn errors of metabolism (IEM) are becoming prevalent in adolescence and adults due to improvements in screening, diagnosis, and management. The appearance of symptoms in adolescence or adulthood is because of the residual enzyme activity that allows for the slow accumulation of toxic molecules over time. They can be encountered in puberty in the form of development-related issues secondary to endocrinial involvement, which may be complications from a previously diagnosed IEM of childhood-onset. This article highlights the common inborn errors of metabolism in the adolescent and pubertal age group and their systemic and endocrinological consequences, especially on gonads, growth, and fertility. The emphasis is given to red-flag findings on history and physical examination indicating a possible inborn error of metabolism for timely diagnosis and management. A multidisciplinary approach with the collaboration of metabolic specialists can play a pivotal role in guiding the families with the correct approach in the right direction.

INTRODUCTION

Inborn errors of metabolism (IEMs) are a group of approximately 1000 monogenic disorders caused by inborn defects in metabolism of amino acids, lipids, carbohydrates, and nucleic acids. In most instances, the underlying cause is the inheritance of a mutated enzyme, normally required for the conversion of one metabolite to another or of a mutated transport protein, which assist the compounds to enter the cell membrane in normal condition. The affected enzyme or co-factor in a biochemical pathway leads to an accumulation of a substrate or toxic metabolite and concurrent deficiency of end product. Individual IEM is a rare disorder, most having an incidence of less than 1 per 100,000 births. However, the collated incidence is approximately 1 in 800 to 1 in 2500 births. These are classified into three subgroups pertinent to their mechanisms: (i) cellular intoxication due to defect in intermediary metabolic pathways resulting in accumulation of toxic compound proximal to block e.g., urea cycle disorders, amino acid disorders; galactosemia; (ii) deficiency in energy production or utilization e.g., mitochondrial disorders, fatty acid oxidation disorders; and (iii) Complex molecules involving organelles e.g., lysosomal storage and peroxisomal disorders. IEMs can present in utero; in newborns, or in children, adolescents, and adults. The rationale behind the late presentation of these disorders is due to some residual activity of the deficient enzyme that allows for the slow accumulation of toxic molecules over time and absence of symptoms till adolescence or adulthood. In this article, we are going to discuss the most common IEMs presenting in the adolescent and pubertal phase and their impact on development. Timely diagnosis of these disorders in this transition period can play a significant role in their management as treating clinicians can plan the multidisciplinary management and guide the family about future prospects and planning in the availability of correct diagnosis. Many of these disorders can be managed through modified diets, enzyme replacements, or supplements.

GENETICS OF IEM'S

IEM's are essentially monogenic disorders and are usually inherited in an autosomal recessive pattern. However, inheritance may be dominant (only one copy of the mutated gene is needed) or sex-linked (the mutated gene is carried on a sex chromosome) in some cases.

In autosomal recessive IEMs, a genetic condition can occur when the child inherits one copy of a mutated gene from each parent. The parents of a child with an autosomal recessive condition usually do not have the condition. Unaffected parents are called carriers because they each carry one copy of the mutated gene and can pass it to their children.

X-linked IEMs can be either dominant or recessive. In X-linked recessive disorders, both copies of the X chromosome must be mutated to have the affected status. Females are usually carrier and asymptomatic due to having two copies of X chromosome. In contrast, males are affected because their single X chromosome carries the mutation. X-linked dominant disorders are the result of a mutation to the X chromosome that can affect either males or females equally and more severe phenotype in males due to single X chromosome.

Mitochondrial IEMs can be due to mutations in either the mitochondrial DNA or nuclear DNA. The IEM’s due to mutations in mitochondrial DNA are transmitted by maternal inheritance, and those due to mutations in nuclear DNA may follow an autosomal dominant, autosomal recessive, or X-linked pattern of inheritance.

IMPACT OF IEM ON PUBERTAL DEVELOPMENT

These disorders have clinically variable and multisystemic presentations, most of which overlap with more common nonmetabolic disorders leading to misdiagnosis in many instances. Moreover, the clinical features in the late-onset forms tend to be less severe than early-onset forms and thus, leading to diagnostic challenges in this particular development.
age group14. However, the acute illness episodes and endocrinological consequences can worsen during the pubertal and adolescent development phase leading to consequences like delayed or precocious puberty, menstrual and menstruation issues, and growth failures. Almost all the glands can be affected due to interference with the hormonal milieu in three ways 1) accumulation of toxic substrates like metals (iron, Copper), complex molecules (Sphingolipids, Galactose, very-long-chain fatty acids); 2) Energy deficiency (Respiratory chain defects); 3) Defect in hormone synthesis or transport. All these mechanisms lead to delayed pubertal development or growth problems and other medical consequences (Table 1).

**CLINICAL FEATURES OF IEMS**

The system-wise clinical features of IEMs in adolescents are:

**CNS manifestations:**
Recurrent episodes of acute neurological dysfunction15,16, seizures17,18, Severe hypotonia19, myopathies19, Spastic paraparesis19, peripheral neuropathy19, movement disorders7 (chorea, parkinsonism, tics or myoclonus) or psychosis and other atypical psychiatric manifestations19.

**Hepatomegaly and gastrointestinal manifestations:**
Hepatomegaly with hypoglycemia9, cholestatic jaundice with failure to thrive, hepatic steatosis, hepatosplenomegaly, recurrent diarrhea secondary to malabsorption16,17.

**Cardiac manifestation:**
Some IEMs may present with the predominantly cardiac manifestation of heart failure due to dilated hypertrophic cardiomyopathy and electrical conduction disorders19.

**Endocrinological manifestations:**
The function of almost all the glands can be impaired due to different pathophysiological mechanisms. They can lead to disturbance of the hypothalamo-pituitary-gonadal axis by causing pituitary insufficiency, gonadal failure, adrenal failure ultimately leading to delayed or precocious puberty, menstrual irregularities, azoospermia short stature, and infertility at a later age. Other manifestations can be diabetes, thyroid, and parathyroid gland dysfunctions which can further affect pubertal development16,18.

**Red flag signs for inborn errors of metabolism:**
1. Consanguineous parents
2. History of similarly affected close family member or sibling or males only (X-linked recessive)
3. Dietary history like aversion to protein diet (Urea cycle disorders, amino acid metabolism disorders)
4. Aversion to sweets or fruits or recurrent hypoglycemic symptoms (Disorders of gluconeogenesis and glycogen storage disorders)
5. Unexplained episodic symptoms or appearance of symptoms more after fasting, exercise, fever (Urea cycle disorder, Amino acid metabolism disorders, Glycogen storage disorders)
6. Multisystemic involvement (Mitochondrial disorders, Lysosomal storage disorders)

The detailed discussion of all the IEMs is beyond the scope of this article. Thus, we have discussed the most common IEMs, their common clinical features, pathophysiology, diagnosis, and management aspects in the tabulated form (Table 1) given below.

### Table 1: Common IEMs in adolescents: Classification, clinical features, effect on puberty, diagnosis and management20

<table>
<thead>
<tr>
<th>Classification</th>
<th>Clinical features</th>
<th>Features affecting puberty/adolescence</th>
<th>Pathophysiology</th>
<th>Diagnosis</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hemochromatosis</td>
<td>Pigmented skin, HSM, Joint pains, CM, cirrhosis, HCC</td>
<td>Hypopituitarism-40% hypogonadotropic hypogonadism in males Adrenal insufficiency</td>
<td>Pituitary ironoverload</td>
<td>Transferrin saturation Serum ferritin HFE gene mutation</td>
<td>Phlebotomy Iron chelation Androgens (Ma y increase risk of HCC)</td>
</tr>
<tr>
<td>Galactosemia</td>
<td>ID, Cataracts Osteoporosis</td>
<td>Premature ovarian insufficiency-75-96%</td>
<td>Accumulation of galactose-1-phosphate and galactitol inducing follicle apoptosis and ovarian tissue alteration Deficiency of UDP-galactose alters glycosylation leading to impairing FSH activity</td>
<td>Galactose and galactitol in blood/urine GALT enzyme and gene mutation</td>
<td>Galactose-free diet HRT Osteoporosis prevention Recombinant FSH Oocyte cryopreservati on</td>
</tr>
<tr>
<td>Complex molecule disorders</td>
<td>*Fabry disease</td>
<td>Gaucher disease</td>
<td>Niemann Pick disease type B</td>
<td>Cystinosis</td>
<td>Congenital Disorders glycosylation (CDGs)</td>
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<td>Acroparasitias in boys Angiokeratomata Stroke Renal, heart and eye involvement</td>
<td>Glucosidase deficiency, infertility, osteoporosis Female-menstrual disorders (9%), abortions</td>
<td>Anemia Thrombocytopenia, bony fractures HSM</td>
<td>HSM pulmonary fibrosis</td>
<td>Adrenal failure</td>
<td>Sphingomyelin accumulation in lysosomes</td>
</tr>
<tr>
<td>Males: Subclinical oligo/asthenozoospermia, infertility, osteoporosis Female-menstrual disorders (9%), abortions</td>
<td>Glucosidase deficiency, infertility, osteoporosis Female-menstrual disorders (9%), abortions</td>
<td>Delayed menarche, menorrhagia</td>
<td>Bone marrow HPL Beta glucocerebrosidase in leukocytes GBA gene mutation</td>
<td>Hypogonadism 66% Erectile dysfunction (66%) Small testes (58%) Primary adrenalin failure (12%)</td>
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<tr>
<td>Loboside storage lysosomes</td>
<td>Alpha-galactosidase A gene mutation in males GLA gene mutation in female (X-linked) epsilon (Fabryzme/R)</td>
<td>Glucocerebrosides accumulation in lysosomes</td>
<td>Bone marrow HPL Beta glucocerebrosidase in leukocytes GBA gene mutation</td>
<td>Sphingomyelin accumulation in lysosomes</td>
<td>Cystine in lysosomes</td>
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<td>Recombinant enzyme replacement therapy (Fabryzyme/R eplagal)</td>
<td>Bone marrow HPL Beta glucocerebrosidase in leukocytes GBA gene mutation</td>
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<tr>
<td>N-glycosylation diseases: serum transferrin isoelectrofocusing O-glyosylation disorders: apo CII isoelectrofocusing Gene mutation</td>
<td>Impaired protein glycosylation leading to fibrosis of gonadal and other tissues</td>
<td>Impaired protein glycosylation leading to fibrosis of gonadal and other tissues</td>
<td>Impaired protein glycosylation leading to fibrosis of gonadal and other tissues</td>
<td>Impaired protein glycosylation leading to fibrosis of gonadal and other tissues</td>
<td>Impaired protein glycosylation leading to fibrosis of gonadal and other tissues</td>
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<tr>
<td>Inhibitors of phosphomannose isomerase under evaluation in CDG-1a Mannose in CDG-1b</td>
<td>Hyponatremia in 74% males Delayed puberty Infertility Growth failure</td>
<td>Height (12%) High (16%) High FSH (32%) High T/ DHT ratio</td>
<td>Height (12%) High (16%) High FSH (32%) High T/ DHT ratio</td>
<td>Height (12%) High (16%) High FSH (32%) High T/ DHT ratio</td>
<td>Height (12%) High (16%) High FSH (32%) High T/ DHT ratio</td>
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<td>Oligospermia</td>
<td>Hypogonadism (66%) Erectile dysfunction (58%) Small testes (12%) Primary adrenalin failure (70%)</td>
<td>VLCFA causes demyelination</td>
<td>Low T (12%) High (16%) High FSH (32%) High T/ DHT ratio</td>
<td>High VLCFA ABCD 1 gene mutation</td>
<td>Low VLCFA ABCD 1 gene mutation</td>
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<tr>
<td>Hearing loss</td>
<td>Hypogonadism (66%) Erectile dysfunction (58%) Small testes (12%) Primary adrenalin failure (70%)</td>
<td>VLCFA causes demyelination</td>
<td>Low T (12%) High (16%) High FSH (32%) High T/ DHT ratio</td>
<td>Height (12%) High (16%) High FSH (32%) High T/ DHT ratio</td>
<td>Height (12%) High (16%) High FSH (32%) High T/ DHT ratio</td>
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<tr>
<td>Ovarian dysgenesis</td>
<td>Fatty-acids accumulation</td>
<td>Leukocyte HSD17b4 gene mutation, or mitochondrial DNA mutation</td>
<td>Inhibitors of phosphomannose isomerase under evaluation in CDG-1a Mannose in CDG-1b</td>
<td>Inhibitors of phosphomannose isomerase under evaluation in CDG-1a Mannose in CDG-1b</td>
<td>Inhibitors of phosphomannose isomerase under evaluation in CDG-1a Mannose in CDG-1b</td>
</tr>
<tr>
<td>Males-Primary hypogonadism Female- PCOS and hirsutism, hypothyroidism, abnormal breast development, precocious puberty endometriosis, irregular menses amenorrhea</td>
<td>Defective ciliary function and transport</td>
<td>Leukocyte HSD17b4 gene mutation, or mitochondrial DNA mutation</td>
<td>High TGs Low HDL ALMS gene mutation</td>
<td>High TGs Low HDL ALMS gene mutation</td>
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<td>Symptomatic</td>
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<td>Selenoprotein deficiency disorder</td>
<td>Myopathy, Dermal photosensitivity</td>
<td>Oligospermia</td>
<td>Defective incorporation of selenocysteine Oxidative stress</td>
<td>Low serum T3 and and high serum T4 Reduced selenoprotein concentrations Leukocytes SECISBP2 gene mutation</td>
<td>Selenium supplement not on efficient on hormone thyroid profile</td>
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<tr>
<td>Energy deficiency disorders</td>
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<tr>
<td>Mitochondrial MIDD MELAS</td>
<td>Deafness, pigmented retinitis, Neuromuscular symptoms Kidney insufficiency Maternal inheritance</td>
<td>adrenal insufficiency, hypogonadism, hypopituitarism</td>
<td>Deficient energy production</td>
<td>Blood lactates/pyruvate ratio Blood 5-OH butyrate/acetoacetate ratio CSF lactates Urine organic acids Plasma amino acids: high alanine and proline Muscle biopsy Mitochondrial DNA study Mitochondrial DNA or WFS1 gene study</td>
<td>Cocktail therapy</td>
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<td>Kearns-Sayre syndrome DIDMOAD</td>
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<td>Fatty acid oxidation disorders</td>
<td>Recurrent hypoglycemia Hepatomegaly</td>
<td>Hypogonadotrophic hypogonadism Hypopituitarism Short stature 30 to 50%</td>
<td>Deficient energy production</td>
<td>Hypoketotic hypoglycemia Plasma acylcarnitine study HADHA Gene mutation</td>
<td>MCT oil</td>
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<td>LCHAD</td>
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<tr>
<td>Glycogenosis</td>
<td>Liver involvement Infections in type Ib Renal complications in adulthood</td>
<td>Adults: I, III types: PCOS, diabetes Type VI, IX: Delayed puberty</td>
<td>Energy deficiency due to defective breakdown of glycogen</td>
<td>hyperplasia, hyperlactataemia, hyperuricaemia, gene mutation</td>
<td>Frequent food intake, uncooked corn-starch, G-CSF in Ib type, allopurinol Avoid OC pills</td>
</tr>
</tbody>
</table>

ADVANTAGES OF GENETIC DIAGNOSIS OF INBORN ERRORS OF METABOLISM IN ADOLESCENTS

Positive impact on pubertal issues:
Early diagnosis can help in management plans and prevent and further worsening of the disease status e.g. Iron chelation or phlebotomy in hemochromatosis, Enzyme replacement therapy in Gaucher disease can reduce the menstrual complaints.

Pregnancy:
Pregnancy was a contraindication in patients suffering from these disorders. Currently, the literature is full of successful pregnancy outcomes in many IEMs; though this has increased challenge to the treating clinician as exacerbation of symptoms may occur during pregnancy due to metabolic decompensation. Moreover, the consequences of the accumulation of toxic metabolites that cross the placental barrier on the growing fetus can be grave if the diet is not taken care of in an IEM pregnancy. Common examples are urea cycle disorders and phenylketonuria which require strict watch over serum ammonia and phenylalanine levels respectively. Clinicians can plan the multidisciplinary approach for the management of such pregnancies if aware about the exact diagnosis.

Reproductive counseling:
All the affected patients with inborn errors of metabolism are at risk to have an affected child because the great majority of them are autosomal recessive or X-linked conditions. The specific risk will depend on the condition, gender of the fetus (for X-linked disorders), partner's family history and ethnicity, and population carrier rates. Genetic counseling and required testing are strongly recommended for all adolescents with an IEM. Reproductive options like prenatal diagnosis, pre-implantation genetic diagnosis, adoption, and use of a surrogate can be discussed and well planned in advance.
Effect on mental health:
By virtue of their presentation, a large percentage of patients with neurological features and psychosis are seen and managed by neurologists or psychiatrists. Early detection of causes can guide treating Physicians in planning the specific treatment because patients with IEMs may show sensitivity to antipsychotics, treatment resistance, and development of metabolic adverse effects. The symptoms may be corrected with simple dietary modifications or replacements in many of these disorders.

Impact on secondary education:
Adolescents transitioning to adulthood have to make decisions regarding higher educational and vocational career paths. They choose the career which they can pursue later without health complications.

Effect on economic resources management:
Dietary management, specific enzyme replacement, and gene therapy treatments are available now for many inborn errors of metabolism like amino acid metabolism, glycogen storage disorders, organic acidurias, lysosomal storage disorders. Some of these may be very expensive leading to financial burden. Family can arrange or plan sufficient funds in advance from some funding organizations or state government agencies depending upon the policies.

CONCLUSION:
Inborn errors of metabolism presenting in adolescence often are missed due to their low prevalence and high clinical variability. The signs and symptoms of IEMs may be nonspecific and often overlap extensively with more common disorders. Identifying red-flag signs and symptoms of an IEM is an essential skill for clinicians. When clinical suspicion of an IEM arises, screening biochemical genetic laboratory studies must be ordered in conjunction with a metabolic specialist for specific diagnosis. IEM if diagnosed and treated early, not only has a better prognosis but also can offer appropriate genetic counseling regarding pubertal development and other future aspects of fertility-related issues and prenatal diagnosis for their families.

REFERENCES:
Reproductive maturity in human beings is termed as puberty. It involves both physical as well as psychosocial changes among both men and women. In girls, sexual maturity is attained between the ages 10-14 and in boys it is 12-16. In girls, the primary signs of maturity are development of breasts, hair growth in arm pits and groin areas and menstruation. In boys, it begins with the increase in size of testicles and penis, hair growth in the pubic area of armpits and growth of muscles, deepening of voice and development of facial hair.

Hypothalamic Pituitary Gonadal (HPG) axis controls both puberty and the functioning of reproductive system. Gonadotropin releasing hormone (GnRH) stimulates pituitary gland to the release Follicle stimulating hormone (FSH) and Luteinizing hormone (LH). These two hormones stimulate ovaries/testicles to synthesize and release sex steroid hormones (estrogens/androgens). In childhood, GnRH pulse generator is slow but one year prior to puberty it works faster and stimulates release of FSH and LH. FSH stimulates oogenesis in females and spermatogenesis in males. The main function of LH is to stimulate production of progesterone in females and testosterone in males. These hormonal changes lead to puberty among both males and females.

GENES REGULATING PUBERTY

Instead of tight hierarchies, regulatory gene networks determine the timing of puberty. These networks are made up of several functional modules that operate in overlapping partially redundant pathways. Various genes are involved in the regulation of these cellular networks, as well as the regulation of the pubertal process. The Kiss1/Kiss1R (kisspeptin) system is an important part of the HPG axis and is required for pubertal onset. Various gene mutations have been discovered in the past that alter the GnRH, which is responsible for the onset of puberty. In a previous whole-exome sequencing study of 15 families with history of premature puberty, 40 members showed mutations in the MKRN3 gene that lead to early activation of HPG axis. Previous genome-wide association studies have also found that single nucleotide polymorphisms (SNPs) near LIN28B altered the age of menarche. LIN 28B is a regulator of microRNA processing and is considered an important genetic regulator of puberty timing.

There was a SNP identified at LIN28B, which was found to have strong association with alteration in age during puberty. About 97 genomic loci were identified in association with adiposity and about 97 SNPs were found to be associated with the variance in adult BMI. It was extrapolated that there is 2.4% of variance in women as compared to only 0.8% in men with respect to waist-to-hip ratio adjusted for BMI. In this study, 697 independent signals at 423 loci in association with adult height were also identified. In another GWAS study, “Tanner puberty stages” were studied and it was identified that LIN28B locus is strongly associated with age at menarche in women and puberty in both boys and girls. Other genes regulating puberty via GnRHI axis are neurokinin B (TAC3), GNRH1. Rare mutations in RNF216 and OTUD4 leads to ubiquitination which can cause hypogonadotropic hypogonadism. In a recent GWAS study, puberty timing, adiposity and adult height was taken into consideration. In the study, it was observed that there are 123 independent signals at 106 genomic loci in association with age at menarche.

It has been reported that there is a strong association between BMI and age at menarche. Genetic co-regulation between age at menarche and BMI involves association of various genes which includes FTO, SEC16B, TMEM18, NEGR1, TNN3K, GNPD2. In all these genes, there is a correlation between BMI increasing allele and age at menarche. Though there are some exceptions like MC4R reports largest estimated effect on BMI but is not associated with age at menarche.

Recent GWAS study has shown that there is a strong association between epigenetic mechanisms and puberty. Both DNA methylation and histone modification are potentially effecting onset of puberty and attainment of sexual maturity.

CONCLUSION

Genetic studies help us in better understanding of biological mechanisms involved in puberty timing. Extensive and vast studies involving signalling pathways, genetic mutations in genes associated with puberty timing is needed to extrapolate the genetic perspective of various mechanisms involved in puberty and disorders.

REFERENCES
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Wellness

PRE-CONCEPTION
- General Karyotyping
- Bad Obstetric History (BOH) Karyotyping – For Couple
- Y chromosome microdeletion (YMD)
- Sperm DNA Fragmentation Assay
- Endometrial Receptivity Test

PRE-IMPLANTATION
- Pre-Implantation Genetic Screening (PGS)
- Pre-Implantation Genetic Diagnosis (PGD)

PRE-NATAL
- Non-Invasive Pre-Natal Test (NIPT)
- Amniocentesis FISH
- Amniocentesis Karyotyping
- Prenatal diagnosis for Genetic Disorders and Syndromes

POST-NATAL
- Abortus Karyotyping
- Abortus FISH (5 Probes)
- Five Probe Chromosomal Involvement (13,18,21,X,Y)
- Cocktail Probe (13,21 or 18,X,Y) – FISH
- Karyotyping for Screening of Genetic Disorders

PEDiatric
- Karyotyping for Screening of Genetic Disorders
- DMD Mutation Analysis
- Mutation analysis for SMA
- Mutation analysis for Thalassemia
- Factor II mutation study
- Factor V Leiden mutation study
- Fragile X mutation analysis

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