Review Article

Contemporary issues in precocious puberty

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ABSTRACT

Precocious puberty poses significant diagnostic and therapeutic challenge to the physician. Recent advances in the understanding of pathophysiology of precocious puberty have resulted in improved management. Timely intervention is mandatory to achieve successful outcome. The identification of critical role of KISS-1-kisspeptin-GPR54 system has gone a long way to provide an insight into pubertal physiology. It is likely that the system would become an important diagnostic and therapeutic target in children with precocious puberty. Epidemiological studies point toward earlier thelarche. This is, however, associated with slower progression as the age of menarche is static. These changes have led to suggestions of lowering the age cutoffs for precocious puberty in girls. New developments in assessment of precocious puberty including gonadotropin releasing hormone (GnRH) agonist test have made characterization of precocious puberty easier. Longstanding GnRH analogs have become the mainstay of treatment of gonadotropin-dependent precocious puberty, while aromatase inhibitors and inhibitors of sex hormone action are increasingly being used in gonadotropin-independent precocious puberty.

Key words: GnRH analog, precocious puberty, recent advances

Introduction

Precocious puberty, premature development of secondary sexual characteristics, represents a significant diagnostic, psycho-social and therapeutic challenge for the physician. Recent advances have enhanced the understanding of pathophysiology and epidemiology of precocious puberty and have translated into improved management. Timely diagnosis and careful clinical assessment, however, remains pivotal to successful management of the condition.

Contemporary Issues in Pathophysiology

The understanding of pubertal regulation has undergone a sea change with the discovery of the KISS-1-kisspeptin-GPR54 system [Figure 1].[1] Before the identification of the system, gonadotropin releasing hormone (GnRH) secreting neurons in the hypothalamus were considered the chief regulator of pubertal onset. GnRH acts on anterior pituitary to induce the secretion of gonadotropins, luteinizing hormone (LH) and follicle stimulating hormone (FSH), which in turn stimulate sex steroid production by gonads.[2] While this GnRH–gonadotropin–sex hormone model explained most issues related with pubertal regulation, some key questions remained unanswered. Firstly, the mechanism of regulation of GnRH neurons via central and peripheral regulators of pubertal onset was unclear. Moreover, the mediator of effects of nutritional signals on pubertal onset was not identified. These lacunae are highlighted by the fact that no cause was identified in over 90% children with hypogonadotropic hypogonadism and 95% girls with gonadotropin-dependent precocious puberty.

Genome wide search in kindreds of patients with hypogonadotropic hypogonadism revealed inactivating mutation in the G protein-coupled receptor, GPR54, as a cause of delayed puberty.[3] The ligand of this receptor

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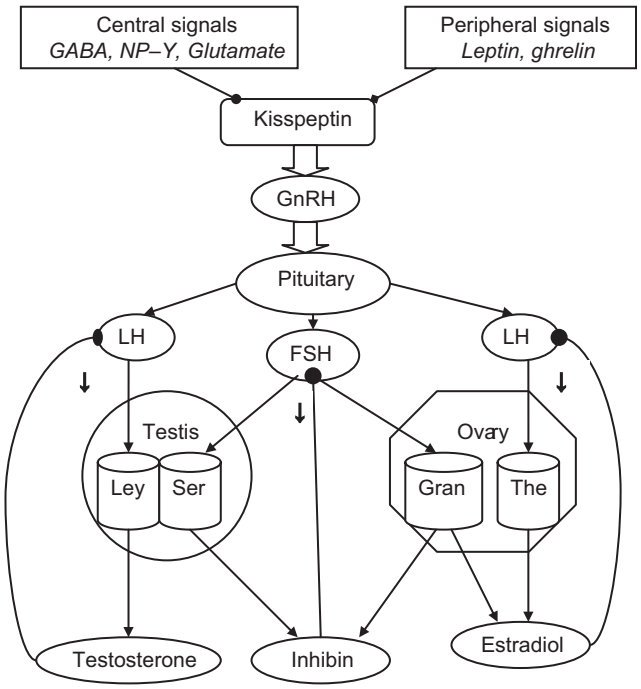

Figure 1: Hypothalamic–pituitary–gonadal axis. Kisspeptin is the key regulator of the onset of puberty by stimulating gonadotropin secretion. (Adapted from Bajpai A, Menon PSN, Regulation of puberty, In Essential Endocrine Disorders, Eds- Desai M, Menon PSN, Bhatia VL, II Edition, Orient Blackswan Publishers, Chennai, 2010)

was identified as kisspeptin, a peptide initially identified as a metastasis suppressor agent.[4] Subsequently, KISS-1 neurons were identified in the arcuate and anteroventral periventricular (AVPV) nucleus of the hypothalamus. The expression of KISS-1 mRNA and GPR54 receptor correlates with the onset of puberty.[5] The identification of GPR54 receptors in the GnRH secreting neurons, synapses of central regulatory neurons with kisspeptin neurons and ghrelin and leptin receptors in KISS-1 neurons confirmed the role of kisspeptin in pubertal regulation.[6,7] The identification of activating GPR54 mutation as a cause of precocious puberty has further strengthened the role of kisspeptin in pubertal regulation.[8] The KISS-1-kisspeptin-GPR54 system is thus the gatekeeper of puberty and central to the regulation of pubertal onset and progression.[9] This axis is a potent target for diagnostic and therapeutic advances in precocious puberty.

Contemporary Issues in Epidemiology

Conventionally, precocious puberty has been defined as the onset of breast stage II development before the age of 8 years in girls and genital stage 2 development before 9 years in boys.[10] The timing of onset of puberty in girls has been decreasing all over the world.[11] This secular trend, first recognized in the developed countries, has been noted in developing countries as well.[12] This has been attributed to improved nutrition and effects of environmental endocrine disrupters. In a study conducted in a pediatric outpatient setting in the United States, as many as 4.5% of girls attained thelarche before the age of 7 years and 8% by the age of 8 years.[13] However, the tempo of pubertal progress is slower and the difference between thelarche and menarche appears to have become longer. The mean age at attainment of testicular volume of 4 mL in boys has not changed significantly and is largely constant at 11.4 years.

These studies led to the recommendation by the Lawson Wilkins Pediatric Endocrine Society to decrease the age "cutoff" for precocious puberty to thelarche before 7 years in White girls and to 6 years in African American girls, whereas no change was suggested for boys.[14] The applicability of these guidelines in Indian girls is unclear in the absence of similar population-based data. Girls born small for gestational age are predisposed to the development of early puberty especially if they have rapid catch-up growth during early childhood.[15]

Contemporary Issues in Etiology

Precocious puberty represents increased sex hormone production by the gonads either independently [gonadotropin-independent precocious puberty (GIPP)] or under the effect of gonadotropins (gonadotropin-dependent precocious puberty).[16] Most girls with precocious puberty have gonadotropin-dependent etiology, while GIPP is commoner in boys. Over 90% girls with gonadotropin-dependent precocious puberty have no identifiable neurological cause. The case is reverse in boys who are more likely to have an underlying cause for central precocious puberty [Figures 2 and 3]. Organic pathology is, however, more likely in Indian children as highlighted by a study where 16 out of 77 (20.8%) girls with gonadotropin-dependent precocious puberty had an organic pathology.[17] Importantly, organic pathology was identified in as many as seven girls with gonadotropin-dependent precocious puberty presenting after the age of 6 years.

Contemporary Issues in Assessment

The aim is to exclude a life-threatening disease and identify the need for urgent management to prevent deleterious effect on growth, reproduction and behavior. The key questions to be addressed include the following.

Is this precocious puberty?

Confirmation of precocious puberty is mandatory to avoid unnecessary investigations and treatment. A significant proportion of children presenting with concerns of early

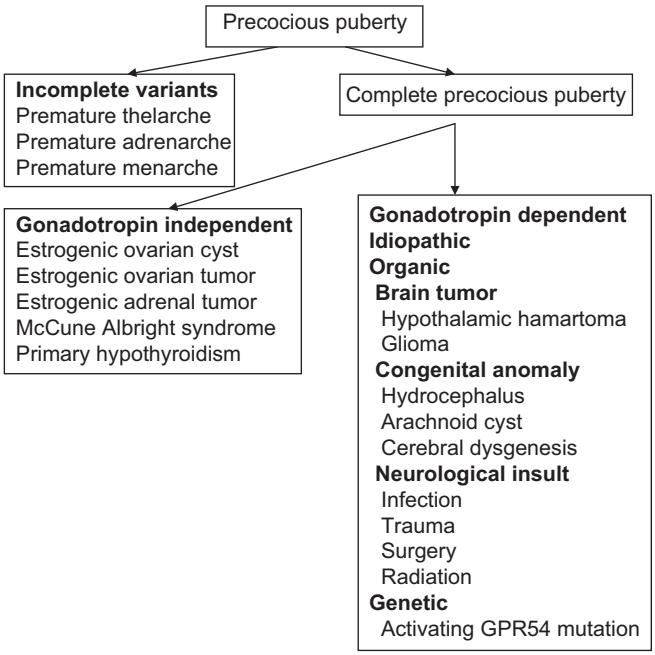

Figure 2: Etiology of precocious puberty in girls

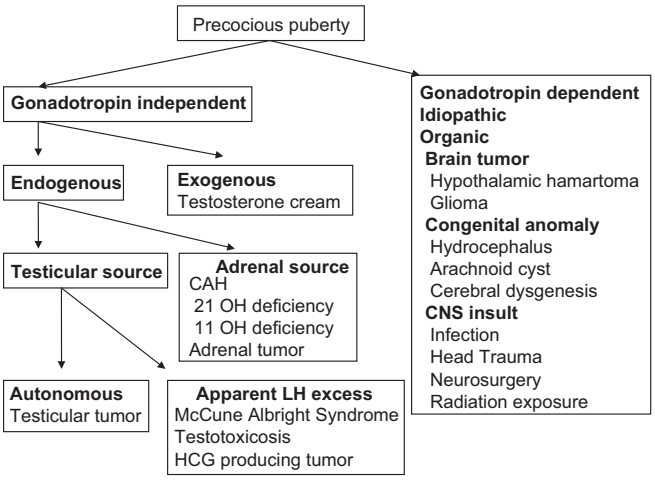

Figure 3: Etiology of precocious puberty in boys

pubertal development represent physiological variations that do not require treatment. The differentiation of lipomastia from thelarche is particularly important in obese girls. Inspection of vaginal mucosa is a reliable indicator of estrogenic status, with red, glistening mucosa suggesting pre-pubertal state and pale mucosa indicating estrogen exposure. Bone age and uterine ultrasound are vital in confirming the progressive nature of precocious puberty. Tubular uterus with no visible endometrial stripe is suggestive of pre-pubertal state, while pubertal state is characterized by pear-shaped structure and endometrial thickness greater than 3 mm. Estradiol levels above 10 pmol/L and testosterone levels in the pubertal range are indicative of pubertal development in boys and girls, respectively.

Table 1: Comparison of isolated thelarche and atypical precocity

Feature	Isolated thelarche	Atypical precocity
Onset	Usually before 2 years	Usually after 2 years
Growth	Normal	Accelerated
Course	Non-progressive	Progressive
Gonadotropin	High FSH, normal LH	High LH and FSH
Bone age	Normal	Advanced
Pelvic ultrasound	Pre-pubertal	Pubertal changes
Treatment	None required	GnRH analog

Table 2: Diagnostic assessment of a girl with isolated pubarche

DHEAS	Testosterone	Probable diagnosis
Mildly elevated	Low	Premature pubarche
Elevated	Mildly elevated	Congenital adrenal hyperplasia (measure 17-OHP)
Significantly elevated	Elevated	Adrenal tumor (ultrasound)
Normal	Significantly elevated	Ovarian tumor

DHEAS: Dehydroantrostenidione sulphate

Is this complete or incomplete precocious puberty?

This is particularly relevant in girls as incomplete variants are common. *Isolated thelarche* is characterized by normal growth, isolated FSH elevation with prepubertal LH levels, age-appropriate skeletal maturation and small ovarian cysts on ultrasound [Table 1].[18] Onset before 3 years of age is frequently associated with regression over 1–3 years. Later onset usually represents slowly progressive form of precocious puberty. *Isolated pubarche* is a benign condition requiring no treatment. The condition, however, needs to be differentiated from other causes of androgen excess, including non-classical congenital adrenal hyperplasia and androgen producing adrenal or ovarian tumors [Table 2]. *Isolated vaginal bleeding* without significant breast development is unlikely to be due to an endocrine cause and should prompt evaluation for local pathology including infection, foreign body, abuse and rarely tumors.

Is this gonadotropin-dependent or -independent precocious puberty?

Testicular volume is the most important indicator for etiology of precocious puberty in boys. Boys with gonadotropin-dependent precocious puberty have pubertal testicular volume (more than 4 mL), while pre-pubertal testicular volume is characteristic of GIPP. Boys with isolated "apparent LH excess" [human chorionic gonadotropin (HCG) secreting tumor, GIPP] have smaller testes for the same pubertal status compared to those with

gonadotropin-dependent precocious puberty. Discordant pubertal development (vaginal bleeding within 1 year of breast development) indicates hyperestrogenic state due to ovarian cysts, McCune Albright syndrome or hypothyroidism.

GnRH-stimulated gonadotropin level remains the gold standard for differentiating gonadotropin-dependent and -independent precocious puberty. The development of third-generation assays for gonadotropin levels has prompted the use of basal gonadotropin levels in diagnosing gonadotropin-dependent precocious puberty. LH is a better indicator of pubertal status compared to FSH as it shows greater increase during puberty. Basal LH of more than 0.6 IU/L and LH to FSH ratio of more than 1 are suggestive of gonadotropin-dependent precocious puberty. Recently, basal LH levels greater than 0.1 IU/L were shown to have sensitivity of 94% and specificity of 88% for gonadotropin dependent precocious puberty.[19] The specificity was increased to 100% using a cutoff of 0.3 IU/L although at the cost of lower sensitivity. GnRH stimulation test is required if baseline gonadotropin levels are inconclusive. Different protocols are available for the test measuring 2–7 samples after injection of intravenous or subcutaneous GnRH (100 g). Pubertal LH levels (>5 U/L) and LH to FSH ratio of more than 0.9 are diagnostic of central precocious puberty.[20] Blunted response is pathognomonic of peripheral precocious puberty. The difficulties in procuring GnRH have led to the development of GnRH agonist test in the assessment of pubertal disorders. Recently, the test has been found to have good diagnostic accuracy with the use of single sample after administration of GnRH agonist, Triptorelin (100 μg subcutaneously).[21] The role of allopregnenolone and kisspeptin as markers of gonadotropin-dependent precocious puberty remains speculative at the moment.[22,23]

Is there a serious underlying cause for precocious puberty?

The main aim of evaluation of gonadotropin-dependent precocious puberty is the identification of an underlying organic etiology. High resolution magnetic resonance imaging (MRI) of the hypothalamic–pituitary region is desirable; however, computerized tomography scan may be considered if MRI is not feasible. Currently, CNS imaging in central precocious puberty (CPP) is recommended in girls with the onset of pubertal changes before the age of 6 years.[24] Studies have, however, indicated that neurogenic etiology may be present in girls with pubertal onset, between 6 and 8 years of age.[25] The need for CNS imaging should therefore be individualized according to the age at onset, rate of progression and neurological features. CNS imaging is mandatory in boys with CPP where the likelihood of organic pathology is very high. Thyroid profile and ovarian and adrenal imaging should be done in girls with GIPP [Figure 4]. In boys with pre-pubertal LH levels, imaging for adrenals and estimation of 17 hydroxyprogesterone (17-OHP) and 11 deoxyxortisol (11-OHDOC) should be done [Figure 5]. Blood HCG levels should be estimated if these investigations are non-contributory. Testotoxicosis should be considered in boys presenting with peripheral precocity at an early age after exclusion of adrenal pathology or HCG secreting tumor.

Contemporary Issues in Management

The aims of management include treatment of the

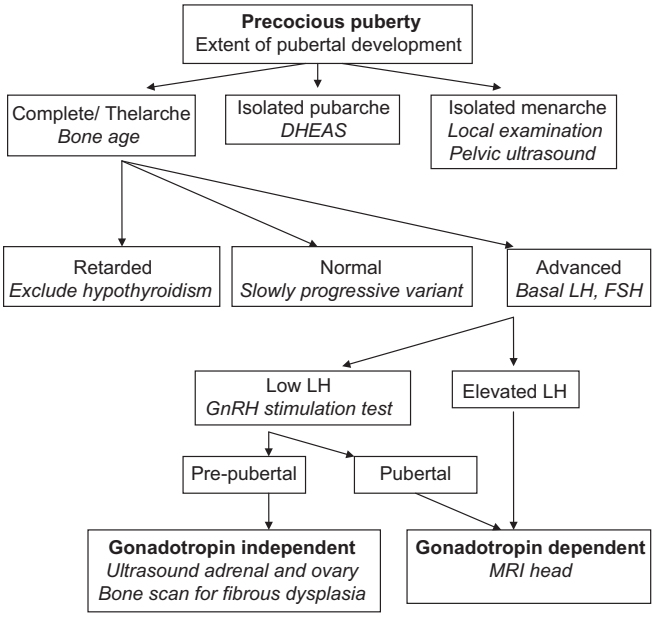

Figure 4: Approach to a girl with precocious puberty

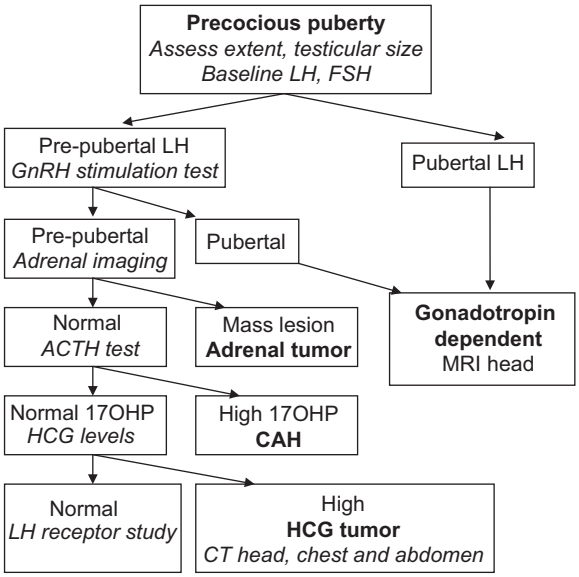

Figure 5: Approach to a boy with precocious puberty

underlying cause, attainment of target height and amelioration of psychological distress. The major concern is compromised final height due to advanced skeletal maturation. Although these children appear tall for age, the height for bone age is compromised. Height deficit in untreated gonadotropin-dependent precocious puberty is in the range of 8–12 cm in girls and 12–20 cm in boys.[26] Increased risk of early intercourse, substance abuse and worse academic achievement have been identified in a subset of children with precocious puberty.[27]

Treatment of Gonadotropin-Dependent Precocious Puberty

Efforts should be directed toward correction of the underlying cause. Neurosurgery is indicated for CNS tumors with the exception of hypothalamic hamartoma, which is a benign condition. These treatments, however, do not reverse the pubertal changes and endocrine intervention is required in addition in most cases.

Medroxyprogesterone acteate

Medroxyprogesterone acetate (10 mg once a day) may be used if treatment with GnRH analog is not feasible. Importantly, the drug does not increase the growth potential of the child. Injectable medroxyprogesterone (50 mg monthly) is commonly used in girls with intellectual disability and precocious puberty where auxological concerns are minimal.[28]

Cyproterone acetate

Cyproterone acetate is an anti-androgen with antigonadotropic properties. It causes regression of secondary sexual characteristics, but has no effect on the prospects for height gain.[29]

Longacting GnRH analogs

GnRH analogs have been developed by chemical modification of the GnRH molecule to ensure prolonged receptor occupancy culminating in prolonged duration of action. Continuous as against pulsatile GnRH exposure desensitizes the pituitary, resulting in reduced gonadotropin production and reversal of pubertal changes.

Indications

The decision for treatment should be individualized based upon age at presentation and extent of growth acceleration. The benefit of this therapy has been clearly demonstrated in girls with onset of puberty before the age of 6 years and those with significant bone age advancement and height compromise. In girls presenting with precocious puberty between the age of 6 and 8 years, GnRH analogs should be considered in the presence of advanced skeletal maturation (height standard deviation score for bone age less than −2) and compromised final height (predicted height below the target height range). GnRH analog may also be considered for psycho-social reasons.

Preparations

Intranasal GnRH analogs have been replaced by longacting depot preparations. These agents have the advantage of prolonged duration of action and need to be administered monthly [Table 3]. Sustained release depot preparations of gosorelin, triptorelin and leuprolide acetate have also been developed, which can be administered after 3–6 months.[30] Once-yearly implants of GnRH analog, histrelin, have also become available in the United States and represent a major advancement in management of the condition.[31] Conventional protocol is to start with monthly injections and assess adequacy of suppression after three doses. If suppression has been achieved, 3-monthly injections can be started with periodic assessment of adequacy of suppression. The dose of leuprorelin required for gonadal suppression is unclear, with higher doses employed in the USA (7.5 mg monthly) compared to European countries (3.75 mg monthly). This was addressed in a trial comparing the effect of 7.5 mg leuprolide monthly against 11.25 mg and 22.5 mg 3-monthly in girls with gonadotropin-dependent precocious puberty.[32] The study demonstrated that at 6 months, greatest suppression was observed in the 22.5 mg group, but the effects were similar at 1 year. Thus, the initial use of higher-dose leuprolide may be worthwhile, particularly in girls weighing more than 30 kg.

Table 3: Comparison of GnRH analog preparations

Preparation	Route	Dose	Frequency	Brand
Naferelin	Nasal	1 puff	Daily	Synarel
Triptorelin	IM	60 μg/kg	Monthly	Triptorelin 3.75 mg
Leuprolide acetate	IM SC	300 μg/kg	Monthly	Leupride depot 3.75 mg
		900 μg/kg	3-monthly	Leupride depot 11.25
Gosorelin acetate	SC	3.6 mg	Monthly	Zoladex 3.6 mg
		10.8 mg	3-monthly	Zoladex implant
Histrelin	Implant		Yearly	

IM: Intramuscular, SC: Subcutaneous

What is New in Precocious Puberty?

- KISS-1-Kisspeptin-GPR54 system is the key regulator of pubertal onset.
- The age at thelarche is decreasing around the world.
- GnRH agonist test has emerged as a reliable test for hypothalamic-pituitary-gonadal function.
- Longer acting GnRH analog depot preparations are effective in gonadotropin dependent precocious puberty.
- Aromatase inhibitors, anti-androgens and selective estrogen receptor modulators are effective in gonadotropin independent precocious puberty.

Follow-up

Patients on GnRH analogs should be followed up 3-monthly for pubertal status and growth parameters. Treatment is expected to result in cessation of pubertal development, but may not cause regression of all features. GnRH analog treatment has no effect on pubic hair development as it is controlled by adrenal androgens. Initial flare-up following GnRH analog may result in advancement of pubertal changes and rarely withdrawal of vaginal bleeding. Cyproterone acetate or medroxyprogesterone acetate may be combined with GnRH analog during the first 3 months of treatment to avoid the flare-up response. Good compliance to GnRH analog is mandatory as delay in treatment may result in resensitization of gonadotropes to GnRH and may cause flare-up response with the next dose.

Adequacy of treatment is assessed by demonstration of pre-pubertal LH levels in response to GnRH stimulation test performed 6-monthly (peak LH less than 2 IU/L).[33] Given the difficulties in procuring native GnRH and the need for separate intravenous injection, measurement of LH levels after GnRH agonist injection has been evaluated. LH levels below 6 IU/L, 2 hours after longacting GnRH agonist, indicates adequate gonadal suppression.[34] Children with inadequate gonadal suppression on 3-monthly injections should be shifted to monthly injection. If the suppression still remains inadequate, the frequency of injections should be increased. Bone age should be obtained annually and used for prediction of final height.

Discontinuation of treatment

GnRH analog should be continued till the age of 10 years in girls and 12 years in boys.[35] Discontinuation of treatment results in gradual reappearance of secondary sexual characters. Menarche is usually attained around 12–18 months following discontinuation of treatment.[36]

Effect of treatment

The efficacy of GnRH analog in improving the final height is difficult to estimate. Most girls attain height in the target height range with an increase over the projected height at initiation of treatment by 8–12 cm.[37] In 87 girls with idiopathic gonadotropin-dependent precocious puberty, GnRH analog treatment for 3–8 years was associated with adult height being 9.5 ± 4.6 cm higher than the predicted adult height at the onset of treatment.[38] Similar findings have been observed in an Indian study of 30 girls with gonadotropin-dependent precocious puberty treated with GnRH analog, triptorelin, where a height gain of 6.4 cm compared to pre-treatment predicted adult height was observed, after a mean treatment of 3.7 years.[39]

Adverse effects

GnRH analog treatment has been found to be safe in a large number of subjects. The treatment is associated with decrease in growth velocity, which may occasionally drop down to pathologically low levels. It is important to exclude growth hormone (GH) deficiency in girls who show significant deceleration in growth following GnRH treatment. GnRH analog treatment may theoretically cause decreased bone mineral density due to decreased estradiol levels. While this adverse effect has not been observed in most studies,[40] calcium supplementation (1 g calcium carbonate every day) should be given to all girls on GnRH analog. There is no increased risk of polycystic ovarian disease, obesity and compromised reproductive potential.

Future directions

Combination of GH and GnRH analog: GH has been used to counter growth suppression induced by GnRH analog.[41] While the role in children with underlying GH deficiency is clear, the effect on GH sufficient children is modest.

Combination of oxandrolone and GnRH analog: Oxandrolone, a non-aromatizable androgen, has been found to be an effective alternative to GH in countering GnRH analog associated growth deceleration.[42] This, however, needs to be studied in detail before implementing in routine clinical practice.

Combination of GnRH agonists and antagonists: GnRH analog treatment is associated with flare-up in the pubertal development in the initial phase due to agonist action. This can result in enhanced bone age and vaginal bleeding. Addition of GnRH antagonists to GnRH analog in the initial phase has been tried to counter these effects. Studies have shown that three doses of certorelix, a GnRH antagonist, 72 hours apart administered with GnRH analog are associated with reduced flare response as indicated by urinary gonadotropin levels.[43] The implication of this in routine clinical practice, however, remains unclear.

Gonadotropin-independent precocious puberty

Treatment of GIPP is directed toward correction of the underlying cause and suppression of sex steroid production or action.

McCune Albright syndrome

Main indication of treatment is reversal of pubertal changes and compromised height. Treatment strategies include the use of medroxyprogesterone acetate (10 mg once a day); ketoconazole (400–600 mg/day in four divided doses) and spironolactone (2–4 mg/kg/day). Testolactone (40 mg/kg/day), an aromatase inhibitor, has been found to be effective in reversing pubertal changes; the need for frequent dosing limits its widespread use.[44] Third-generation aromatase inhibitors such as letrozole and anastrazole have been

increasingly used in the condition.[45] Letrozole, but not anastrazole, has been shown to be effective in controlling bone age maturation and vaginal bleeding.[46] However, the drug has been linked with rupture of ovarian cysts. Studies on tamoxifen, a selective estrogen receptor modulator, have also been encouraging.[47] GnRH analog treatment is indicated in girls with triggered gonadotropin-dependent precocious puberty.

Functional ovarian cyst

Most ovarian cysts regress spontaneously and do not require surgical intervention. Patients with complex ovarian cysts (size greater than 8 cm or multiseptate cysts) should undergo estimation of tumor markers (beta-HCG and alpha-fetoprotein) and laparotomy. Thyroid functions should be assessed in all girls with ovarian cysts before performing extensive investigations and surgery.[48]

Congenital adrenal hyperplasia

Physiological glucocorticoid therapy is effective in retarding the pubertal progress in boys with the condition. However, diagnosis is often delayed in most patients, resulting in triggered gonadotropin-dependent precocious puberty. These children should be treated with GnRH analogs. Combination of GnRH analog and growth hormone treatment may be required in the presence of severely compromised growth potential.[49,50]

Testotoxicosis

Treatment with aromatase inhibitor, testolactone, and ketoconazole has been disappointing. Combination of anastrazole and anti-androgen biclutamide has recently been shown to be effective.[51]

Conclusions

There have been tremendous advances in the understanding of pathophysiology and therapeutics in precocious puberty. It is likely that these advances will result in better patient management and outcome of these patients in the near future.

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