A Review on Update on Diagnosis and Therapeutic Management of Precocious Puberty''- Along with A Case Report

Kulvinder Kochar Kaur[1]*, Allahbadia GN[2] and Singh M[3]

[1]Kulvinder Kaur Centre for Human Reproduction, India

[2]Rotunda-A Centre for Human Reproduction, India

[3]Consultant Neurologist, Swami Satyanand Hospital, India

*Corresponding author: Kulvinder Kochar Kaur, Scientific Director, Dr Kulvinder Kaur Centre for Human Reproduction 721, GTB Nagar Jalandhar-144001, Punjab, India, Tel: 91-181-9501358180; Email: kulvinder.dr@gmail.com

Abstract

Precocious Puberty (PP) is the attainment of secondary sex characters before the age of 8 in girls and 9 yrs in boys. It can be divided into Central PP(CPP)/True PP or Gonadotropin dependent PP and Gonadotropon independent PP(GIPP) or Pseudo PP. CPP is characterized by the premature activation of the hypothalamo-Pituitary-Gonadal Axis. Onset of secondary sex characteristics before age 8, which further progresses with increased growth velocity and bone age acceleration which ultimately ends in impaired adult height. Mutation studies have shown occasional mutations in KISS1. KISS1R, Makorin ring finger protein 3(MKRN3) genes as some of the genetic modifications. Treatment with Gonadotropin releasing hormone agonists remain the treatment of choice which helps in ultimate attainment of normal height till actual age of puberty. With further introduction of a yearly GnRH subcutaneous implant histerelin administration has become more convenient than the tedious monthly GnRH a in the form of leuprolide depot or decapeptyl depot. This review sums up the various causes of CPP and GIPP with an update of its management, differential diagnosis and a case report to highlight an example.

Keywords: CPP; GIPP; KISS1; KISSR1; MKRN3mutations; GnRHa; Leuptolide depot; Histrelin implant; Bone age

Introduction

Initiation of Puberty (Central Control Mechanism)

Factors governing the neuroendocrine switch'' for the pulse generator, which is on 'in early infancy, then turns off during childhood, and switches back 'on' again at puberty have not been found. The list of factors which modulate the activity of the hypothalamo-Pituiary – Gonadal (HPG) Axes includes both inhibitory and excitatory neurotransmitters and peptides as per studies on nonhuman as the models. The GnRH neurosecretory neurons are located in the mediobasal hypothalamus of primates and the preoptic region in rodents [1,2]. Changes in GnRH secretion depend on transsynaptic [3] and glial [4] inputs to the GnRH neuronal network. Trans synaptic changes involve an increase in excitatory input

and a reduction in inhibitory influences [1], the glial component is mainly facilitator and secreted both by growth factors and small molecules that directly or indirectly stimulate GnRH secretion [4]. The excitatory transsynaptic regulation of GnRH secretion is given by at least 3 different neuronal subsets: kisspeptin neurons acting via GPR54 receptors [5], glutamatergic neurons acting mostly via AMPA receptors [6,7] but also by NMDA receptors[7,8] and GABA acting via inotropic GABAA receptors [8]. The inhibitory component of this circuit depends mainly on GABA ergic neurons acting via GABA B metabolic receptors [9], but also by opiatergic neurons which use different peptides and different receptors for inhibitory transmission [reviewed in 1].

The complexity of this cellular network suggests that there is no definite pathway or cellular subset responsible for regulatory gene networks which control neuroendocrine control of puberty [10-12]. Rather initiation of this process may need regulatory gene networks controlled by a small group of upstream genes[10],Some of these central regulators have been found in the POU domain gene Oct2,homeodomain gene Ttf1/Nkx2.1 and a novel zinc finger containing gene called enhanced at Puberty(EAP1) [13]. Although monogenic mutations which affect GNRHR [14], GPR54 [15,16], KISS1 [17], Tac3 and TACR3 [18]=> pubrteal failure these are not the only puberty relevant genes as a genome wide association studies have shown that variants of >30 genes are associated with the age at menarche in humans [19]. Lomniczi et al. showed that an epigenetic mechanism of transcriptional repression times the initiation of female puberty in rats. They identified silencers of Polycromb group (PcG) are major contributors to this mechanism, and showed that PcG proteins repress Kiss1, a puberty activating gene. Hypothalamic expression of two key PcG genes Eed and Cbx 7 decreases and methylation of their promoter increase preceding puberty. Inhibiting DNA methylation blocks both events and thus results in pubertal failure. The pubertal increase in Kiss1 is accompanied by EED loss from the Kiss1 promoter and enrichment of histone H3 modifications associated with gene activation. Preventing the eviction of EED from the Kiss1 promoter disrupts pulsatile GnRH release, delays puberty, and compromises fecundity. Thus they concluded epigenetic silencing is a novel mechanism which underlies the neuroendocrine control of female puberty [20].

Rhie at al. aimed to determine whether serum kisspeptin may function as a marker of CPP by investigating serum kp levels in Korean girls with CPP (n=30) and age matched healthy prepubertal controls (n=30) were measured by competitive enzyme immunoassays. Skp levels were significantly higher in CPP group than in the control group (4.61+-1.78 vs2.15+-1.52p M/L, p<0.001). SKp was positively correlated with peak LH, peal /basal LH ratio and peak LH/FSH ratio during GnRH stimulation test. CPP is supposed to be triggered by premature increase of Kp. SKp may be used as a marker of CPP. Further studies on KISS 1 gene polymorphisms leading to high risk of premature increase of Kp and upstream regulators of Kp are also needed were their conclusions [21].

Gamma amino butyric acid (GABA) is an inhibitory neurotransmitter produced by specialized neurons in the hypothalamus. They have an important role in regulating the activity of the pulse generator .Hypothalamic perfusion studies have indicated that release of GABA into the median eminence decreases as pulsatile GnRH secretion increase at the onset of puberty. On the other hand central perfusion with a GABA a antagonist (bicuculline) or the antisense oligo deoxynucleotide for the mRNA Coding the GABA A synthesizing enzyme glutamine acid decarboxylase (GAD) stimulates GnRH release. Chronic administration of bicuculline into the 3rdventricle induces precocious puberty and menarche in prepubertal female monkeys. Changes in the subunit composition of GABA A receptors may contribute to the disinhibition of pulsatile GnRH secretion at the onset of puberty. Thus central GABA signaling is one of the factors which restraints GnRH neuronal activity in childhood.

Neuropeptide Y

NPY is a hypothalamic peptide which is basically involved in the control of food intake behavior and reproductive function in adults. Intra cerbroventricular administration of NPY in adult castrate female monkeys inhibits pulsatile GnRH release. In males the postnatal pattern of pulse generator is inversely related to NPY gene and protein expression in the medial basal hypothalamus and central administration of an NPY antagonist stimulates GnRH release in juveniles. Thus like GABA, NPY is an important neurobiological brake which restrains the GnRH pulse in the prepubertal primate. Yet others have found that NPY levels increase at puberty, infusion of NPY into the median eminence increases GnRH release while giving NPY antiserum into the median eminence did not stimulate GnRH release in prepubertal monkeys. Freitas et al. studied 33 patients with gonadotropin dependent precocious puberty, 22 with HH, and 50 controls. On genomic DNA extraction, NPY Y1R

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gene sequence analysis, cell surface expression and functional activity of an identified receptor variant showed that a heterozygous substitution of lysine (K) by threonine (T) at position 374 in the carboxyl terminal region of NPY Y1R was identified in a girl with familial GDPP. Her mother, who had pubertal development at appropriate age, carried the same genetic variant. Introduction of the K374T variant into an expression vector containing the human NPY Y1R complementary DNA led to a partial reduction in cell surface expression of NPYY1R in transiently transected HEK293 cells. This mutation did not lead to a significant reduction in NPY stimulated activity of the receptor in this heterologous expression system. No other allelic variants of the NPY Y1R gene were identified in controls. Hence they concluded that a new inherited heterozygous variant of the NPYY1 R gene in a girl with PP had been identified however this most likely did not contribute to her phenotype. Mutations of the highly conserved NPYY1R gene do not appear to represent a frequent mechanism underlying human idiopathic central pubertal disorders [22].

Precocious Puberty

Puberty onset is induced by the initial detection of an increase in amplitude and frequency of gonadotropin releasing hormone (GnRH) pulses after a long period of quiescence in the childhood period. Once Pulsatile GnRH secretion emerges it=>raised gonadotropin secretion, which includes follicle stimulating hormone (FSH), luteinizing hormone (LH) by the pituitary gland, which ultimately => gonadal function [23]. If this Hypothalamo-Pituitary-Gonadal (HPG)axes is activated it causes gonadotropin dependent precocious puberty, which clinically is defined as the development of secondary sexual characters before 8 yrs in girls and 9 yrs in boys. There is complex interactions among genetic, nutritional environment and socioeconomic factors [24,25]. Disadvantages of early puberty are risks of early age of menarche in girls are greater incidence of breast cancer, obesity, type 2 DM, and cardiovascular disease [19]. It Also affects conduct and behavior disorders during adolescence [26].

Genetic factors influence timing of puberty [27]. This is exemplified by similar age of menarche in mothers and daughters, besides among members of same ethnic groups and more chances of concordance of puberty timing between monozygotic than dizygotic twins [28-30]. 27.5% of CPP are familial, suggesting autosomal dominant transmission with incomplete sex dependent penetrance as shown by familial studies [31].

Although increasing number of genes have been implicated in congenital isolated hypogonadotropic hypogonadism and in the Kallmann Syndrome [32-34], only a few rare molecular defects have been found in patients with central precocious puberty and no strong association has been proved [22,35-38]. Only 2 mutations ,one mutation in the gene encoding Kisspeptin (KISS1) and the one encoding its receptor (KISS1R) have been associated with CPP, even after screening a relatively long cohort of patients for mutations in these genes, which indicates that isolated mutations in KISS1 and KISSR genes are uncommon causes of CPP] [39,40]. Abreu et al. performed whole exomic sequencing in 40 members of 15 families with CPP Candidate variants were confirmed with Sanger sequencing. They also performed real time PCR assays to detect levels of mRNA in the hypothalami of mice at different ages. They found novel heterogenous mutations in the MKRN3, the gene which encodes makorin Ring finger protein 3, in 5 of the 15 families, with both sexes being affected. The mutations included three frame shift mutations, predicted to encode truncated proteins, and one missense mutation, predicted to disrupt protein function. MKRN3 is a paternally expressed, imprinted gene located in the Prader Willi Syndrome critical region (chromosome 15q11-q13). All affected persons inherited the mutations from the fathers, a finding that indicates perfect segregation with the mode of inheritance expected for an imprinted gene. Levels of Mkrn3 mRNA were high in the arcuate nucleus of prepubertal mice, decreased immediately before puberty and remained low after puberty. Thus they concluded that MKRN3 causes CPP in humans [41].

PP can be classified as:

Gonadotropin dependent PP: Is characterized by both breast and pubic hair development in girls and by pubic hair development and testicular enlargement (>4ml in vol or 2.5cm in diameter) in boys. The early developments of sexual characteristics are isosexual i.e. consistent with the Childs gender.

Gn Independent PP also called Peripheral PP or pseudo PP describes early sexual development that is independent of GnRH and gonadotropins and generally results from exposure to sex steroid hormones that derive from the gonad, the adrenal or the environment. Gn Independent PP is further sub-classified as isosexual with secondary sexual characteristics consistent with the

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gonads and as contra sexual when inconsistent with gender virilization in girls or feminization in boys.

Incomplete PP describes children with isolated premature thelarche or premature adrenarche.

Both Gn dependent PP and CPP results from early maturation of the HPG axis and is more common in girls than in boys. Although puberty begins earlier than normal, the sequence of pubertal events generally is normal and proceeds at normal pace. Upto 90% of children with CPP have no identified cause (idiopathic), a diagnosis made by exclusion. However the disorder can be associated with a variety of CNS lesions, including tumors, irradiation, hydrocephalaus, cysts, trauma, inflammatory diseases and midline defects like septooptic dysplasia. The findings that TGFα accumulates in areas of brain injury as a result of trauma induced activation of gene expression in glial cells, presents an intriguing model that TGFα stimulates GnRH release [42]. Thus head MRI is indicated when there are no neurological signs or symptoms. Tumors associated with CPP include hamartomas, astrocytomas, ependymomas, pineal tumors and optic and hypothalamic gliomas. Hamartomas are heterotopic neuronal masses containing GnRH neurons which typically attach hypothalamic generator divorced from the central inhibitory mechanisms which normally restrain activity during childhood; they are most common tumors associated PP and can be associated with gelastic seizures (laughing, giggling), some produce TGFα, which mediates release of GnRH. Hamartomas can produce GnRH pulses, just like the normal hypothalamic tissue from which they are derived. In addition hamartomas can also produce TGFα which in turn stimulates GnRH release [43]. The PP, which is observed in children with neurofibromatosis usually relates to optic glioma.

Activating mutation in the gene encoding the KISS1R mediates the action of Kisspeptin (an excitatory neuroregulator) of GnRH dependent PP.

Children exposed to high circulating androgens or E2, as may occur with CAH, virilizing tumors and the McCune Albrights syndrome often exhibit early maturation of HPG axis, which then results in CPP.

Although very rare girls with severe primary hypothyroidism can present with PP exhibiting breast development, galactorrhea and episodic menstrual bleeding. In most girls the high S.TSH, which has structural similarity to FSH appears to activate the FSH R.

Raraly Gn Dependent PP has resulted from autonomous pituitary gonadotropin secreting tumor rather than from early maturation of HPG axis.

Gonadotropin Independent Precocious Puberty (GIPP): GIPP may occur because of increased sex steroid secreted from the gonads or adrenals or from exposure to exogenous E2. Autonomous functional ovarian follicular cysts are the most common causes of GIPP [44]. In girls transient breast development and vaginal bleeding are the most common presentation, which can be an isolated event or recur at unpredictable levels. SE2 levels typically are increased but not always (due to the regression of the cyst) and both basal and GnRH stimulated gonadotropin concentration are low. The cysts may enlarge and involute and then recur, so that signs of sexual precocity and vaginal bleeding remit and exacerbate [45]. In most cases bone age is not advanced. Ovarian USG usually shows one or more unilateral or bilateral ovarian cysts>15mm in diameter. This disorder is self limited in most and requires no treatment. However recurrent cysts resulting in prolonged or repeated E2 exposure can precipitate early maturation of the HPG axis=>gonadotropin dependent PP. Autonomous ovarian cysts can also be an early manifestation of McCune Albrights Syndrome, arising before emergence of the characteristic skin (café-au lait spot) or bone lesions affected patients, therefore require careful long term follow up [46].

Ovarian tumours are rare causes of GIPP in girls and include granulosa cell tumors, leydig cell tumors and gonadoblastoma.

McCune Albright Syndrome is a rare disorder characterized by PP, café-au lait skin pigmentation, and polyostosis fibrous dysplasia of bone, all caused by a somatic mutation of the α subunit of the G protein (encoded by the GNAS1 gene), which results in a mosaic distribution of cells bearing constitutively active adenylate cyclase [47]. The mutations =>continuous stimulation of endocrine function and in addition PP also can cause gigantism, Cushing's syndrome, adrenal hyperplasia and thyrotoxicosis in varying combinations. Although PP is the most common clinical manifestation, the phenotype varies with the tissues which are affected by the mutation and can include hepatitis, intestinal polyps and cardiac arrhythmias. It is possible that this mechanism is responsible for the childhood disease other than McCune Albright Syndrome. Because of that it has been suggested that this genetic disorder should be called inherited $G_S\alpha$ deficiency [48]. In keeping with the autonomous nature of gonadal activity, treatment with a

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GnRH agonist fails to suppress gonadal hormonal secretion or reverse the precocious puberty [49]. Just like In the other forms of GIPP, sequence of pubertal development may be abnormal, e.g. vaginal bleeding frequently precedes breast development. The skin and bone lesions may be the original presenting features and may increase over time. If there is early exposure to E2, which is repeated it can =>increased levels of sex steroids and =>increased growth, advanced bone age and reduce adult height; it may also induce early maturation of the HPG axis which =>secondary Gonadotropin Dependent PP. McCune Albright Syndrome is more common in girls than in boys .This diagnosis should be considered in girls presenting with recurrent follicular ovarian cysts and episodic menses. Partial forms of the syndrome have been described.

Familial male PP is inherited in an autosomal dominant fashion and is caused by mutations in the LH receptor gene which =>activation [50]. No effects in females of activation mutatons of either the LH receptor gene or the FSH receptor gene have been reported. Adrenal pathology like androgen secreting tumors and CAH, is another cause of GIPP.

Exposure to environmental pollutants having estrogenic activity (xenoestrogens) can result in premature sexual development in infants or toddlers .They can be accidental exposure to estrogens, xenoestrogens, placental extracts contained in cosmetics or personal hair care or skin care products and environmental pollutants which can act as endocrine disruptors by mimicking E2 like polychlorinated bisphenyls, pesticides and plasticizers which may be found in water contaminated with industrial products. Serum hormone levels in children typically are in normal range but may vary depending on the nature, type and frequency of use or exposure. Important point is that children are very sensitive to the effects of estrogens and may respond with increased growth or breast development even if serum levels are below the detectable limits.

Diagnosis of Precocious Puberty

Cause may be obvious by history or physical examination; familial occurrence might rule out a tumour. Clinically nature of precocity dictates certain diagnostic priorities

- Rule out life threatening disease; including neoplasms of the CNS, ovary and adrenal

- define the velocity of the process; is it progressing or stabilized; management is based on this.
- isolated nonendocrine causes of vaginal bleeding (trauma, foreign body, vaginitis ,genital neoplasms should be excluded. Differential Diagnostic Steps

Physical diagnosis

- Record of growth, Tanner stages, height and weight percentiles
- External gentalia changes
- Abdominal, pelvic, neurological Examination
- Signs of androgenization
- Special findings; McCune Albright, hypothyroidism

Laboratory Diagnosis

- Bone Age
- Head MRI, Ultrasonography(USG) of abdomen and Pelvis
- FSH,LH,HCG assays
- thyroid function tests(TSH and free T4)
- Steroids(S.DHEAS,Testosterone,E2,Pg,17 OH Pg
- Inhibin levels
- GnRH Testing

If the full signs of sexual precocity are present, and basal or Gn RH stimulated gonadotropins are in the pubertal range (FSH>7.5 iu/l and LH>15 IU/L pituitary secretion of Gn's is suspected. Inhibin A and B levels are very low and can be undetectable before puberty but steadily increase during puberty [51]. Any abnormality on neurologic examination or imaging reflects central (CNS in origin)PP, Central MRI is the imaging technique of choice [52]. If examination and MRI are normal, idiopathic sexual precocity is the most likely diagnosis. It is important that basal serum gonadotropins can be in prepubertal range in the early stages of idiopathic or CPP; with time and progression of sexual development these will rise to the pubertal range. An ectopic source of Hcg should be considered if S.Gn's are suppressed and E2 is markedly increased, a situation which can be confirmed by an immunoassay specific for the β subunit of HCG.

The rare feminizing adrenal tumor maybe present if the laboratory picture is more one of increased adrenal androgens, with only slightly increased S.E2and suppressed S.Gn's, abdominal and pelvic USG and imaging are indicated.

When signs of sexual precocity are associated with accelerated growth and sexual maturation in the absence

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of virilization, the etiology may be an ovarian tumor or cyst. A pelvic mass is usually palpable. In this situation, S FSH/LH are suppressed whereas E2 is usually increased .An increased S Pg suggest an ovarian luteoma. Pelvic USG can help to confirm the presence of an ovarian mass. Laporotomy is indicated to confirm the diagnosis as well as to do surgical resection. Adrenal Hyperplasia or a virilizing adrenal or ovarian tumor must be considered if signs of sexual precocity are accompanied by virilization. With elevation of serum 17 OH Pg and adrenal androgens the diagnosis of 21 hydroxylase deficient adrenal hyperplasia is established, whereas an elevation of serum 11deoxy cortisol =>the diagnosis of 11β hydroxylase deficient adrenal hyperplasia. If these 2 serum hormones are normal and S DHAS or T is increased an adrenal tumor or a virilizing ovarial tumor is suspecred.USG and abdominal imaging can be used to localize the tumor.

Breast development usually correlates with a bone age of 11 and menarche with a boneage of 13.If breast development and genitalia development and pubic hair growth and vaginal bleeding are seen in a short child a delayed bone age, primary hypothyroidism is the most likely diagnosis.

This can be confirmed by finding a low S.T4 and raised TSH, concentration. SFSH/LH levels can be in the pubertal range but these will decrease following thyroid treatment. Galactorrhea can be present along with hypothyroidism.

Treatment of Precocious Development

Aims of management
I. Diagnosis and treatment of intra cranial disease
II. Arrest maturation until normal pubertal age
III. Attenuate and diminish established precocious characteristics
IV. Maximize eventual adult height
V. Facilitate the avoidance of abuse and decrease emotional problems and provide contraception if needed.

A lot of therapies have been used to achieve these aims, which include medroxyprogesterone acetate, cyproterone acetate and danazol but besides side effects, bone maturation and growth were not regularly or sufficiently controlled. These drugs have been replaced by use of GnRH analogues for the treatment of true PP.

Short half life of GnRH is because of fast cleavage of bonds between amino acids 5-6, 6-7 and 9-10.Substitution of aa's at position 6 and replacement of the C terminal glycine amide have produced effective GnRH agents. They can be given subcutaneously(s/c), intranasally or in long acting depots. There is not much experience with GnRH antagonists in PP Treatment.

GnRH agonis treatment initially gives a short term "flare" stimulation of Gn release, followed by desensitization and down regulation, yielding a marked decrease in Gn's, steroid production and biologic effects. Marked regression of pubertal characteristics, amenorrhea and reduction in growth velocity are achieved rapidly and maintained within the first yr of treatment [53]. Final bone height is increased but is dependent on the stage at which medication is started, the bone age at which the drug is stopped and the adequacy of dose regimen [54,55]. Maximum height attainment needs early onset of treatment and long duration of treatment [56]. Final height can approximate that of the general population, indicating that growth is programmed early in puberty [57].

Individuals with advanced bone age will achieve >growth, because suppression of gonadal steroids delays epiphyseal fusion and prolongs the duration of growth but treatment is more effective if begun before bone age exceeds 12yr [58].

With idiopathic GDPP, height predictions are more accurate using the Bayley-Pinnerau tables for average girls. Despite the advanced bone age in patients. Some patients show a marked slowing of growth with GnRH agonist treatment and in these patients the addition of growth hormone (GH), produces an excellent growth response [59]. The decision to treat with a GnRH agonistis based primarily in the predicted adult height and progression of pubertal development [60, 61]. Many girls with idiopathic PP do not have a serious impairment of their height potential, because of the very slow progression of their puberty. When the prediction based on bone age indicates deterioration, GnRH treatment can be initiated. GnRH treatment is warranted when sexual maturation and bone age are undergoing rapid progression. The dose of GnRH agonist treatment can be monitored by measuring E2 levels. Because E2 is the hormone that triggers growth and development, the objective is to maintain E2 <10pg/ml, a prepubertal range [62].

Since many commercial E2 assays lack sensitivity in this range, it may be necessary to confirm adequate suppression by demonstrating a lack of Gn response to GnRH. In general, children require higher doses of GnRH

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agonists to achieve suppression, as compared to adults. Even with treatment, adrenarche, will continue probably, true to its independent control system.

Treatment is maintained until the epiphyses are fused, or until appropriate pubertal and chronological ages get matched. Discontinuation of therapy is followed by prompt reactivation of the pubertal processes and the development of regular ovulatory functions in a pattern similar to that of normal adolescents [63]. GnRH agonist treatment is also recommended for the GnRH secreting hamartomas of the hypothalamus [64,65]. The progress of the tumor can be monitored by imaging and risky surgery can be avoided.

Though different formulations and routes of administration exist the most widely used GnRH a has been intramuscular leuprolide depot injection. Since 2007, a s/c implant containing potent GnRH a histrelin has been a popular alternative for the treatment of CPP [66]. Made up of a micro porous hydrogel the implant is surgically inserted just under the skin of the upper arm and continuously released histrelin atleast for one year [67]. Studies in children with CPP have shown complete HPG axis and sex steroid suppression along with improvement in predicted height. Fisher et al studied time to menarche in girls and testicular volume in boys after removal of histrelin implants.

71 patients (56 girls) treated with a histrelin implant were identified from medical records. Of these 36 implanted girls (68%naive) and 6 explanted boys (83% naive) were included in the analysis. Time to menarche after explanations in girls and time to testicular volume increase after explanation in boys were determined. Other variables were indication and duration of treatment, history of menarche (girls), previous therapy and age at beginning of and end of histrelin therapy. Of the girls 30were treated for CPP, 26 had menarche at an average age 12.7 months after explanations. Other 30,7 were treated for other indications, of whom 6 had reached menarche. In girls with CPP, older age at explanation correlation with sooner menarche (p=0.04). Boys achieved spontaneous pubertal enlargement within one yr of explanation. Thus they concluded resumption of puberty after histrelin explanation in treatment naïve and non naïve boys and girls with and without CPP. Menarche in girls with CPP occurs within a similar timing as observed with other treatment approaches [68]. Silvermann et al. conducted a prospective open label phase 3 study to study the efficacy of histerelin implant for determining GnRH a therapy to children with CPP.

36 Children with CPP were eligible to continuous treatment receiving a new implant, upon removal of the prior 12 months histrelin implant during a long term extension phase. Hormone suppression was maintained throughout the study in patients who had prior GnRH a therapy (n=16) and in treatment naïve patients (n=20). Bone age to chronological age ratio decreased from 1.417 (n=20) at baseline to 1.18 (n=8) at 48 months in treatment naïve children (p<0.1).Predicted height in girls increased from 151.9 at baseline to 166.5cm at month 60(n=6;p<0.5),with a 10.7cm ht gain observed among treatment naïve children(n=5).No side effects on growth or recovery of the HPG axis was observed with hormonal suppression. This implant was well tolerated Thus they concluded long term histerelin implant provided sustained Gn suppression safely and effectively and improved predicted adult height in children with CPP [69].

Arcari et al. evaluated 117 Girls with idiopathic CPP (ICPP), who were divided according to pretreatment weight (wt) status in normal wt (NW), overweight (OW), and obese (OB). BMI at one and two yrs of treatment was assessed. BMI-SDS of 60 patients who reached adult height (AH) was compared to that of 33 ICPP untreated girls. NW girls significantly decreased their baseline BMI-SDS at 1 and two yrs of treatment. OW girls only had significant increment at one yr of treatment, while obese girls showed no BMI-SDS change .Patients evaluated at AH (at least 4 yrs after GnRH a withdrawal showed a significant decrease on BMI compared to baseline and significantly lower BMI than the untreated group. Thus they concluded that in ICPP girls the BMI increase under GnRH was inversely related to the pretreatment weight status .In the long term follow up no detrimental effect of GnRH on body weight was observed. BMI-SDS was lower in the treated than in untreated girls [70].

Lazar et al. tried to assess the peevalence of obesity, metabolic outcome (hyperlipidemia, diabetes and hypertension) and malignancy rate of former CPP women between the 3rd and 5th decade of life. It was a case controlled study of a historical cohort using database of a health management organization. The study group comprised of 142 CPP patients aged 27-50 yrs (100GnRH analog treated; 42 untreated, while the control group comprised of 413 women randomly matched for age, year of birth and community clinic (283 for the GnRH treated, 130 for the untreated. They found at young adulthood, BMI (percentile and distribution) of treated and untreated former CPP women was comparable to that of the respective controls. Increased BMI at presentation was a

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risk factor for obesity in adulthood in the GnRH a treated group (r 0.257; p=0.01). Prevalence of metabolic comorbidities (16 vs 13.4%; 21.4vs 24.6%) and malignancy rates (1.0vs 1.5) we similar in the former CPP women and their controls with no statistically significant differences between the 2 groups. Thus they concluded that CPP (treated/untreated) is not associated with an increased risk of obesity, metabolic derangements, or cancer in young adulthood. This gives reassurance regarding health status of former CPP women [71].

GnRH agonist treatment is not effective for the non central forms of PP like McCune-Albrights Syndrome or CAH. However should patients with McCune Albrights Syndrome or CAH mature their HPG axis and develop true sexual precocity, then supplementary GnRH agonists therapy is helpful [72,73]. Primary treatment in these cases is directed towards suppression of gonadal steroidogenesis. Medroxy progesterone acetate can be used in depot form to suppress secretion or an aromatase inhibitor can be given. If a specific etiology for PP is identified treatment is aimed at curing the underlying disorder. Neurosurgical excision of hypothalamus, pituitary, cerebral or pineal tumors must be individualized in each patient. If these tumors are small and do not extend around or into vital brain structures, their removal can be successful. If complete surgical excision is not possible radiation therapy should be considered. Although many tumors are said, not to be radiosensitive, this may be the only treatment available although new chemotherapy protocols are of benefit with some tumors. The tumors which secrete HCG, like chorioepitheliomas, teratomas, hepatomas should be managed in a manner consistent with current specific treatment protocol for HCG secreting neoplasms.

If an ovarian/adrenal tumor is found surgical removal is the treatment of choice. For an ovarian cyst it may be difficult to know whether the cyst is an autonomous source of E2 or whether the growth is secondary to Gn stimulation. GnRH testing is useful in resolving this question. If multiple bilateral cysts are discovered these are usually secondary to central Gn secretion. If the cyst is solitary and the contra lateral ovary appears immature, then cyst resection is justified. With primary hypothyroidism, thyroid replacement therapy prevents further progression of sexual precocity .If adrenal hyperplasia is identified treatment with appropriate doses of glucocorticoids and (mineralocorticoids if salt wasting is present) also prevents further progression of pubertal development. If these patients have a bone age of

11-12 yr, glucocorticoid therapy can result in the onset of true sexual precocity.

Special care is needed for psychosocial problems in these children with precocious puberty. These children have intellectual, behavioral, psychosexual maturation in keeping with their chronological age, not their physical or pubertal age. They do not have early heterosexual activity or abnormal sexual libido. Parent's teachers and peers may have unrealistic expectations of their intellectual or athletic capabilities. Thus counseling of parents and child are important to prevent any psychosocial problems in future life including marital life.

Conclusion

Thus one needs to consider central precocious puberty once one has ruled out all causes pertaining to the causes like hypothyroidism, central neurological causes like hamartoma or any tumour ,rule our ovarian cysts, other causes like McCune Albright syndrome. Test for the known genetic mutations and then if no cause found one tends to label it as idiopathic CPP. Treatment of choice remains GnRH agonists with histrelin implant preferred if available which ensures normal growth velocity and height attainment. Serum Insulin like growth factor 1 and IGF binding protein 3 levels have been found to be raised in these girls with CPP [74].

Case Report

A 21/2 year old female child was brought by parents with history of attainment of menarche. Her delivery had been by LSCS. No history of drug intake by mother during antenatal period was there. There was no history of trauma to the child or no exposure to drugs accidently or by intent. On examination the child had breast development to Tanner stage 2/3, external genitalia were normal although no definite pubic hair were found. Locally hymen was intact and no evidence of injury or foreign body was found. Blood tests revealed normal thyroid function tests ruling out Hypothytoidism, but S.FSH/LH were elevated to 7and 10 iu/l respectively. Bone age studies showed advanced bone age. MRI of the skull did not show any abnormality like tumor or hamartomas.USG of pelvis and abdomen did not show any ovarian cysts or tumors of ovary or adrenal. Hence a diagnosis of idiopathic CPP was made .Because of lack of availability of histrelin implant patient was given injection leuprolide depot 1/4th ampoule and was continued on monthly injections when she got lost to follow up.

Discussion

This is a rare case of CPP presenting at such a young age without any history of head injury or any brain lesions like tumor hamartoma on MRI. No attempts were done to identify any gene mutations like KISS1, MSRN3 because of non availability. Since histrelin implant was not available at that time in india we chose leuprolide depot. Although her FSH/LH/E2 levels suggested idiopathic CPP with normal thyroid function tests and no ovarian cysts one cannot put a diagnosis of idiopathic CPP without genetic tesing. With more advances in the understanding of physiology one may have a possible understanding rather than labeling any disease idiopathic like in this case.

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