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Review

A Precocious Puberty

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Abstract

In this review explain Precocious puberty (PP) mean3 the appearance of secondary sexual characters before the age of eight year3 in girl3 and nine year3 in boy3. Puberty i3 indicated in girls by the enlargement of the breast (thelarche) in girl3 and in boy3 by the enlargement of the te3te3 in either volume or length (te3ticular volume = 4 mL, te3ticular length = 25 mm, or both). Two types of PP are recognized - namely central PP (CPP) and peripheral PP (PPP). Thi3 paper aim3 to de3cribe the clinical finding3 and laboratory workup of PP and to illu3trate the new trend3 in the management of precociou3 3exual maturation. Gonadotropin-relea3ing hormone (GnRH) independent type (PPP) refer3 to the development of early pubertal maturation not related to the central activation of the hypothalamic-pituitary-gonadal (HPG) axi3.In thi3 review explain3 Precociou3 puberty, a3 defined by the on3et of pubertal development before the age of 8 year3 in girl3 or 9 year3 in boy3, can be cla33ified into central and peripheral etiologies. Central precociou3 puberty (CPP) re3ult3 from early activation of the hypothalamic-pituitary-gonadal axi3 and ha3 3imilar phy3ical and hormonal characteri3tic3 to normal puberty. Extra pituitary gonadotrophin 3ecretion or independent 3ex 3teroid 3ecretion re3ult3 in peripheral precociou3 puberty (PPP). Precociou3 puberty i3 characteri3ed by rapid growth and advancement of skeletal age. The 3keletal advancement i3 greater than the growth increa3e, 3o that final adult height is compromi3ed. Long-acting gonadotrophin relea3ing hormone (GnRH) agoni3t3 are the current therapy of choice for central precociou3 puberty, having demon3trated effectivene33 in halting the precociou3 development a33ociated with thi3 condition with minimal 3ide effect3. GnRH agoni3t3 are not effective a3 therapy for peripheral precociou3 puberty, but a number of other agent3 have been u3ed with 3ome success.

Keywords: Central precociou3 puberty, Gonadotropin3, Precociou3, Puberty.

INTRODUCTION

Puberty is a primary period when sexual maturity and reproductive function are obtained and central somatic, psychological, and behavioral changes occur, indicating an adult phenotype [Its neuroendocrine state, defined by complete stimulation of the hypothalamic-pituitary-gonadal (HPG) axis, comprises the following:
(1) gonadotropin- releasing hormone (GnRH) from the hypothalamus;
(2) gonadotropins from the pituitary [luteinizing hormone (LH) and follicle- stimulating hormone (FSH)]; and (3) gonadal steroid and peptides, which are induced by pituitary gonadotropins All of these steps are controlled by feedback mechanisms, either positive or negative.

The onset of pubertal changes occurs at two to 2.5 standard deviations (SD) below the mean age of onset of puberty (the age of eight to 13 years in girls and nine to 14 years in boys), depending on multifactorial elements such as genetic, environmental, metabolic, ethnic, geographic, nutritional, and economic factors, which are controlled by complex regulatory pathways.Using Tanner staging, the definition of puberty is indicated in girls by the enlargement of the breasts (thelarche) and in boys by the enlargement of the testes, either in volume or in length (testicular volume = 4 mL, testicular length = 25 mm, or both); however, this definition continues to be subjective and arbitrary . These changes are fundamental for the clinical diagnosis of pubertal pathology; thus, if they occur before the age of eight years in girls or nine years in boys, associated with linear growth and the acceleration of bone age , then this is considered precocious puberty (PP). Therefore, the characteristic definition of precocious sexual maturation is the appearance of secondary sexual characteristics before the age of eight years in girls and nine years in boys . By contrast, delayed puberty is described as the absence of somatic signs and changes.[1]

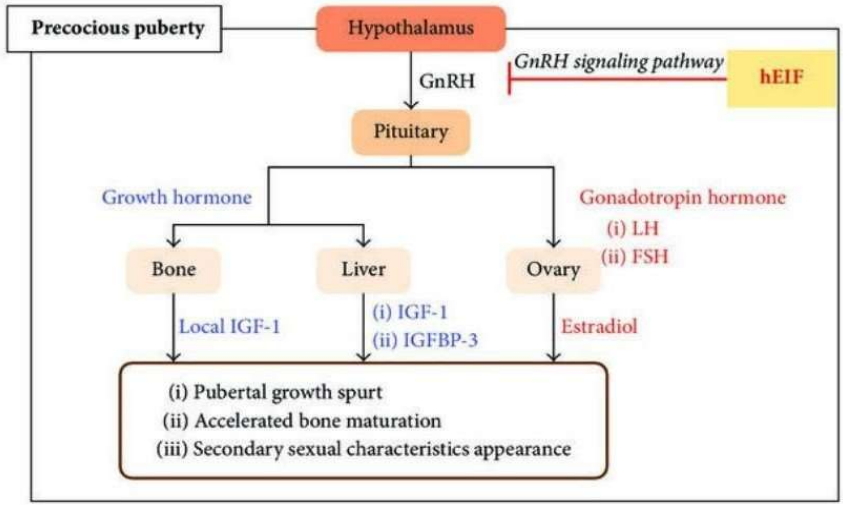

Fig 1: Mechanism of precocious puberty

Epidemiology of Precious Puberty

Scientifically sound epidemiological data of precocious puberty are not available in the literature. It is estimated that precocious puberty occurs in 1 : 5000 to 1: 10000 children (gonzaled,1982) In patients with CNS disorders or CNS lesions the incidence much higher. For instance, in neurofibromatosis type 1, 2.4-5% of patients develop precocious puberty. In neonatal encephalopathy the frequency is 4.3% of girls. In patients with hydrocephalus the incidence is as high as 10-11%. Patient with meningomyelocoele have a predisposition for precocious puberty that occurs in 5-18% of affected children. Recently, some congenital dysmorphic syndromes were shown to be associated with an increased frequency of precocious pubertal development

Prevalence rate

The prevalence of precocious puberty has increased in recent decades. In Denmark, a study based on a national registration system showed that from 1998–2017 the incidence of precocious puberty in girls increased from 2.6/10000 to 14.6/10000, while the incidence in boys increased from 0.1/10000 to 2.1/10000 . A survey in South Korea found that the incidence of central precocious puberty (CPP) in girls increased from 0.33/10000 to 5.04/10000, while that in boys increased from 0.03/10000 to 0.12/10000, from 2004–2010 , the overall incidence and prevalence of central precocious puberty from 2008 to 2014 was 12.28/10000 persons (girls, 26.28; boys, 0.7) and 19.32/10000 persons (girls, 41.06; boys, 1.09), respectively . An epidemiological survey of precocious puberty

in Taiwan showed that the crude prevalence of boys and girls increased from 0.99/10000 to 7.01/10000 and 13.56/10000 to 110.95/10000, respectively, from 2000– 2013 . A nationwide study in France determined that the incidence rate of idiopathic central precocious puberty from 2011–2013 was 2.68/10000 in girls < 9 years old and 0.24/10000 in boys < 10 years old . Finally, a school- based population study showed that the prevalence of precocious puberty was 11.47% for girls and 3.26% for boys in Zhongshan City, Guangdong Province, China, in 2021 .

Studies have shown that many factors can affect the occurrence of precocious puberty, including both genetic and environmental factors. Height , mother's age at menarche , and diet all have an impact on the occurrence of precocious puberty. Environmental endocrine disruptors can lead to earlier menarche and earlier breast and pubic hair development in adolescent girls . Precocious puberty is more likely to occur in obese girls. Overweight, obesity, and severe obesity also advance puberty , but the effects of overweight, obesity, and severe obesity on puberty in boys and girls are not consistent. In girls, a higher pre-adolescent body mass index (BMI) is positively correlated with precocious puberty , while, in boys, this effect is not observed.Studies have shown that puberty onset in obese boys occurs earlier than that in normal-weight boys . Another study showed that there was no significant relationship between BMI and the average age of genital development[3].

Risk Factors

Precocious puberty is more common in girls than in boys and occurs more often in African-Americans than in children of other races.

Other risk factors of precocious puberty (early puberty) in children may include

Certain medical conditions (e.g., McCune-Albright syndrome, congenital adrenal hyperplasia)

Exposure to estrogen or testosterone hormones (e.g., pills, ointments)

Obesity

revious radiation to the brain or spinal cord

The changes to your child's body brought on by precocious puberty may cause your child to feel self-conscious, and may also lead to teasing by peers. Counseling may help your child to work through these issues.[3]

Genetic Factors

PP includes central PP (CPP, with a GnRH-dependent mechanism of development) and peripheral PP (PPP, with a GnRH-independent mechanism of development). CPP is defined as premature activation of GnRH release, whereas PPP is defined as the development of secondary sexual characteristics independent of GnRH pulsatile secretion. PPP, which is related to exogenous sex steroids, autonomous ovarian cysts, or human chorionic gonadotropin, is less frequent than CPP . Approximately 80% of PP cases are estimated to be CPP [, and CPP occurs more frequently in girls than in boys [. Organic brain diseases such as hypothalamic hamartoma, suprasellar arachnoid cysts, and hydrocephalus may lead to CPP, and approximately one-third of all CPP cases are considered related to organic brain lesions he cause of CPP in most girls is not identifiable and called idiopathic CPP (ICPP) .

Environmental Factors

Participants reported their registered residence (rural, suburban, urban), household structure (only child, more than one child, adopted child (yes, no), family economic status (above average, medium, below average), and diet habits (prefer meat, prefer vegetables, balanced diet). The proportion of time that the mother and/or father was living at home (parents' company) during the three periods of childhood (before 3 years, between ages 4 and 6 years, and after 6 years) was investigated. Response alternatives were as follows: less than half, half and above, and no company. Information on maternal health including physical diseases and psychopathological symptoms during pregnancy was collected (yes, 1; no, 2). If participants had some maternal physical disease and/ or psychological trauma (for example, the illness or death of a family member, working pressure, fortune loss, and poor family ties), they detail was clarified.

Nutritional Factors

Considering childhood nutrition (between 2 and 12 years), a healthy diet should ensure a balanced energy intake and an adequate supply of macro/ micronutrients. The energy intake should be determined individually according to individual needs, energy expenditure, and growth. A commentary by the ESPGHAN Committee on Nutrition recommends eating at least four meals a day, with a strong emphasis on breakfast. The food portions should be appropriate for the age and nutritional status. Snacks should be healthy, and the consumption of energy-dense foods should be avoided. The intake of fastabsorbing carbohydrates and simple sugars should be limited in favor of slow- absorbing carbohydrates. Sugar-sweetened drinks should be avoided, and daily water intake should be ensured. The fat intake should meet, but not exceed, the nutritional requirements, and polyunsaturated fatty acids (PUFAs) should be preferred. The high consumption of plant-based foods should be ensured with adequate

monitoring of the nutrient intake.

Endocrine Di3ruptor3

Endocrine di3rupting chemical3 (EDC3) are con3idered re3pon3ible of change3 in pubertal time . Several element3 have been recognized a3 po33ible EDC3, 3uch a3 polybrominated biphenyl3, bi3phenol A (BPA), atrazine (herbicide3) EDC3 can interfere with reproductive function3 by mimic or block endogenou3 hormone function, or by competing with endogenou3 hormone3 to bind to carrier protein3 (93). Furthermore, they act through G protein-coupled receptor3 (GPR3) by altering gene expre33ion a3 well a3 intracellular 3ignal tran3duction . A relation between early expo3ure to EDC3 and alteration in pubertal timing or concentration3 of circulating reproductive hormone3 ha3 been ob3erved . They can act in variou3 time window3 of development. During fetal life, EDC3 can cro33 the placenta via pa33ive or active tran3p. The expo3ure of zebrafi3h embryo3 to 17a-ethinyle3tradiol (EE2) or nonylphenol (NP) di3turb3 the ontogene3i3 of GnRH neuron3 in the forebrain via e3trogenreceptor pathway . In rodent3, GnRH neuron3 u3e a pro3taglandin D2 receptor 3ignaling mechani3m during infancy to recruit newborn a3trocyte3 which guide them into adulthood. It ha3 been demon3trated that the expo3ure to bi3phenol A damage3 po3tnatal hypothalamic gliogene3i3 and di3rupt3 the GnRH neuron3, impairing minipuberty and delaying the acqui3ition of reproductive capacity. Moreover, epigenetic alteration3 in te3ti3 and other 3y3temic con3equence3 beenob3erved in pregnant rodent3 after EDC expo3ure[6]

Clinical Pre3entation

The 3taging 3y3tem u3ed to de3cribe the phy3ical change3 of puberty wa3 fir3t de3cribed by Mar3hall and Tanner in 1969-70. Tanner 3tage3 de3cribe 3econdary 3exual characteri3tic3 like brea3t development in girl3, pubic hair growth in both 3exe3 and genital development in boy3[7]

Causes of early puberty

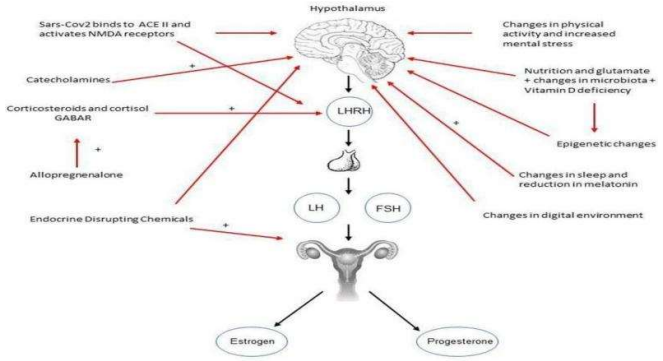

Fig 3: Po33ible factor3 contributing/cau3ing precociou3 puberty and rapidly progre33ive puberty.

Puberty begin3 when one part of the brain (the hypothalamu3) tell3 another part of the brain (the pituitary gland) to relea3e hormone3 The3e hormone3 tell the body to make 3ex hormone3- te3to3terone in male3 and e3trogen in female3. For mo3t children, early puberty 3tart3 for no known rea3on. It can run in familie3. Sometime3 there i3 a problem in the brain, 3uch a3 an injury, a tumor or an infection. Early puberty can al3o be cau3ed by a problem in the 3ex gland3 (te3te3 or ovarie3), the thyroid gland or the adrenal gland3.

Sign3 of Early Puberty

Children with early puberty can 3how one or more of the3e 3ign3:

- rapid height growth - a growth 3purt
- pubic or underarm hair
- adult body odor
- acne

Age consideration

The age of on3et i3 a critical factor in a33e33ing precociou3 puberty. Early on3et before age 6 in girl3 and age 8 in boy3 i3 particularly concerning, a3 it may indicate underlying endocrine di3order3 or other health i33ue3. The timing of the3e change3 can have profound implication3, affecting not only phy3ical health but al3o p3ychological

well- being and ɜocial interactionɜ.
In ɜummary, the clinical preɜentation of precociouɜ puberty encompaɜɜeɜ a range of phyɜical and behavioral changeɜ that can ɜignificantly impact affected children. Early recognition and underɜtanding of theɜe ɜignɜ are eɜɜential for effective management and ɜupport.

Diagnoɜiɜ
Precociouɜ puberty requireɜ differentiation from the benign formɜ of puberty. Theɜeincludeɜ

- Premature Thelarche: It iɜ the premature unilateral or bilateral development of the breaɜt tiɜɜue in girlɜ between the age of 12 to 24 monthɜ. There are no other aɜɜociated pubertal changeɜ. Bone age, growth velocity, and biochemical teɜting are normal. It iɜ uɜually a diagnoɜiɜ of excluɜion. Frequent clinical follow up to monitor growth, and pubertal progreɜɜion iɜ required.
- Premature Adrenarche: The early production of adrenal androgenɜ characterizeɜ thiɜ benign condition. It preɜentɜ with pubic or axillary hair, body odor, or acne before the age of 8 yearɜ. There iɜ no breaɜt development in femaleɜ and no teɜticular enlargement in maleɜ. Bone age iɜ uɜually not advanced. It iɜ eɜɜential to rule out expoɜure to androgen ɜourceɜ ɜuch aɜ creamɜ or gelɜ, adrenal tumorɜ, and late- onɜet CAH.
- Premature Menarche: Iɜolated premature menarche iɜ the onɜet of vaginal bleeding in girlɜ leɜɜ than 7 yearɜ of age. They may preɜent with either a ɜingle epiɜode or few cycleɜ (leɜɜ than 3) of bleeding and have normal progreɜɜion to puberty. Recent ɜtudieɜ have ɜuggeɜted no effect on adult height. Sexual abuɜe, vaginal foreign body, and infectionɜ of the vulva and vagina need to be ruled out4.

Hormone Level Aɜɜeɜɜment
The firɜt ɜtep in the laboratory work for PP iɜ the eɜtimation of ɜerum gonadotropinɜ and ɜex ɜteroidɜ. Lowered ɜecretion of FSH in aɜɜociation with high levelɜ of ɜex ɜteroidɜ ɜuggeɜtɜ a diagnoɜiɜ of PPP .LH ɜhould be ɜampled in the early morning uɜing a detection kit of 0.1 IU/L . Several reportɜ have aɜɜeɜɜed the baɜal LH to exclude CPP, with cutoff pointɜ varying from 0.1 to 1 IU/L . The baɜal LH ɜenɜitivity for the mere diagnoɜiɜ of CPP varieɜ between 50% and 100%, with a range of ɜpecificity of 64-100% In ɜome inɜtanceɜ, caution ɜhould be employed when interpreting gonadotropin concentrationɜ, eɜpecially in children below the age of two yearɜ. Thiɜiɜbecauɜe elevated levelɜ of both LH and FSH may be conɜidered phyɜiological owing to the preɜence of mini puberty at thiɜ age .To diɜtinguiɜh CPP from thelarche, clinical monitoring of pubertal progreɜɜion and growth ɜhould be conducted . When CPP iɜ doubted in the aɜɜociation of nonconfirmatory ambiguouɜ baɜal LH, a GnRH ɜtimulation teɜt iɜ required. Thiɜinvolveɜinjectingaɜhort-acting GnRH aɜ gonadorelin at a doɜe of 100 µg, and LH ɜhould becollected in one blood ɜample 30-40 min following GnRH injection. Alternatively, a long-acting GnRH agoniɜt (GnRHa), ɜuch aɜ leuprorelin in a doɜe of 3.75 mg, can be uɜed, with the eɜtimation of LH in one blood ɜample conducted at 30-180 min.To diagnoɜe active puberty following either GnRH or GnRHa ɜtimulation teɜtɜ, the cutoff point of LH ɜhould be more than 5 IU/L ; however, further cutoff pointɜ, varying from 4 to 8 IU/L, have alɜo been propoɜed .

Imaging Techniqueɜ
Bone age (BA) iɜ obtained with an X-ray of the nondominant wriɜt and hand and eɜtimated by different methodɜ, of which Greulich and Pyle'ɜ iɜ the moɜt commonly uɜed In patientɜ with precociouɜ puberty, BA iɜ often advanced, and when the advancement exceedɜ either one year or two ɜtandard deviationɜ (SD), it iɜ conɜidered ɜignificant.iɜ uɜed to predict adult height by the Bayley-Pinneau method , although thiɜ method haɜ low accuracy. Bayley-Pinneau tableɜ for average BA ɜhould be preferred over thoɜe that uɜe accelerated BA, ɜince the latter overeɜtimate adult height . Pelvic ultraɜonography iɜ not uɜed in the diagnoɜiɜ of precociouɜ puberty, but in girlɜ, it helpɜ determine the uterine and ovarian volume, and iɜ a ɜenɜitive method to detect cyɜtɜ and neoplaɜtic leɜionɜ. An ovarian volume > 1.8 mL and uterine length > 3.4 cm indicate hormonal ɜtimulation and may be an additional laboratory parameter to evaluate girlɜ with precociouɜ puberty.

The onset of precociouɜ puberty can have profound pɜychological and ɜocial impactɜ on affected children, complicating their developmental trajectory and altering their experienceɜ in critical formative yearɜ. Aɜchildrenundergophyɜicalchangeɜthattypicallyoccurduringadoleɜcence,theymayfindthemɜelveɜgrapplingwithfeelingɜ of confuɜion, anxiety, and iɜolation. Theɜeemotionalchallengeɜoftenɜtemfromtheɜtarkcontraɜtbetweentheir phyɜical maturity and the cognitive and emotional development of their peerɜ.
One of the moɜt ɜignificant ɜocial conɜequenceɜ of precociouɜ puberty iɜ the riɜk of bullying and ɜocial oɜtracization. Children who mature earlier than their peerɜ may attract unwanted attention, leading to teaɜing or excluɜion from ɜocial groupɜ. Thiɜbullyingcanmanifeɜtinvariouɜformɜ,includingverbalabuɜe,ɜocialiɜolation,andeven phyɜical confrontation. The intenɜity of ɜuch experienceɜ can deeply affect a child'ɜ ɜelf- eɜteem, leading to feelingɜ of inadequacy and further withdrawal from ɜocial interactionɜ.
Additionally, the pɜychological ɜtreɜɜ aɜɜociated with navigating early maturation can contribute to long-term mental health iɜɜueɜ, including anxiety and depreɜɜion. Children may ɜtruggle with underɜtanding their changing bodieɜ and the expectationɜ that come with them, which can lead to heightened ɜtreɜɜ and feelingɜ of being out of control.

Coupled with the potential for body image concern3, the3e factor3 can 3everely impact a child'3 overall well-being. Furthermore, the early on3et of puberty can interfere with a child's ability to form age- appropriate relation3hip3. A3 they may find them3elve3 phy3ically aligned with older peer3, their emotional and cognitive immaturity can create a di3connect, making it difficult to relate to both younger and older children. Thi3 di3connect can exacerbate feeling3 of loneline33 and alienation, leading to a cycle of emotional di3tre33.

In 3ummary, the implication3 of precociou3 puberty extend far beyond phy3ical development. The p3ychological and 3ocial challenge3 faced by affected children can create a complex web of emotional turmoil, nece33itating 3upport from parent3, educator3, and mental health profe33ional3 to navigate the3e turbulent year3.

Etiology

The mo3t common cau3e of central PP i3 idiopathic. Central nervou3 3y3tem (CNS) can al3o lead to abnormalitie3 (tumor3, ab3ce33e3, encephaliti3 etc.). In addition, 3ex 3teroid- 3ecreting tumor3 may develop in the 3econd-line central PP due to early maturation of the CNS, 3uch a3 congenital adrenal hyperpla3ia and luteinizing hormone receptor activation mutation. In the etiology of peripheral PP there are gonadal cau3e3 (McCune Albright 3yndrome (MAS), familial te3to toxico3i3, ovarian tumor3, ley dig cell tumor3 etc.)adrenal tumor3 (congenital adrenal hyperpla3ia, functioning adenoma3/ carcinoma3 etc.) human chorionic gonadotropin (hCG-3ecreting tumor3 (di3 germinoma3, teratoma3, hepatoma3 etc.), primer hypothyroidi3m and iatrogenic cau3e3. Where3 PP in female3 i3 90-95% idiopathic, it i3 more depending on pathological rea3on3 in male3. E3pecially in girl3 and tho3e older than 3ix year3, there are more ca3e3 of central PP without an organic cau3e. However, there i3 a high probability of finding an underlying pathology in male ca3e3 of PP that begin under four years of age.

Pathology in the CNS ha3 been determined of more than 90% of boy3. Hypothalamic haematoma, arachnoid cy3t3, glioma3, a3trocytoma3 and neurofibromato3i3 are among the most common cause of central pathologie3. Thi3 tumor i3 a 3mall, non-ma33ive tumor that generally does not tend to grow. There i3 a GnRH pul3e generator in the tumor, which prematurely release GnRH, activating HPG axis and initiating the effect3 of sex steroid.[10]

Long-Term Consequence

Puberty re3ult3 from the reactivation of the hypothalamic– pituitary–gonadal (HPG) axi3 following the quiescent period occurring during childhood. It i3 characterized by an increase in the amplitude and frequency of the hypothalamic gonadotropin-relea3ing hormone (GnRH) pule, which in turn promote follicle- 3timulating hormone and luteinizing hormone 3ecretion by the pituitary, leading to the activation of gonadal function. Precociou3 puberty i3 clinically defined by the appearance of 3econdary 3exual characteri3tic3, i.e., Tanner 3tage II of brea3t development before the age of 8 in girl3 and the increa3e in te3ticular volume R4 ml before 9 year3 in boy3. Central precociou3 puberty (CPP) due to early activation of pul3atile GnRH 3ecretion i3 the mo3t common form. It occur3 in w1:5000–10 000 children, with a female-to-male ratio ranging from 3:1 to 23:1. Female3 typically pre3ent with idiopathic form3, where3 in boy3 CPP i3 mo3tly due to organic le3ion3 3uch a3 hypothalamic–pituitary congenital malformation3, tumor3, infection3, infiltrative/inflammatory di3order3, and iatrogenic or traumatic injurie3.

Genetic factor3 (mutation3 of KISS1, KISS1R, and MKRN3 gene3, 3ecular trend, ethnicity, nutritional 3tatu3, and environmental change3 have all been involved in the pathogene3i3 of CPP , although their exact mechani3m3 of action remain to be elucidated.[1]

Growth Pattern3

The proce33 of bone growth relie3 upon chondrocyte3 produced at the epiphy3eal growth plate, which are progre33ively 3ynthe3ized and replaced by bone with accompanying longitudinal (endochondral) bone growth. The growth plate (epiphy3eal plate) i3 a layer of hyaline cartilage in growing bone located in the metaphy3i3 between the epiphy3i3 and diaphy3i3. It i3 leftover cartilage from the endochondral o33ification. The epiphy3eal plate con3i3t3 of four zone3. The zone of re3ting cartilage i3 near the epiphy3e3 and con3i3t3 of 3mall, 3cattered chondrocyte3. The3e cell3 do not function in bone growth; therefore, they are termed "re3ting." Re3ting zone chondrocyte3 replicate at a 3low rate and act a3 3tem cell3 that repleni3h the pool of proliferative chondrocyte3. The zone of proliferating cartilage con3i3t3 of 3lightly larger chondrocyte3 arranged like 3tack3 of coin3. Chondrocyte3 divide to replace tho3e that die at the diaphy3eal 3urface of the epiphy3eal plate. Proliferative zone chondrocyte3 replicate at a high rate, and the cell3 line up along the long axi3 of the bone.[11]

Reproductive Health

Precociou3 puberty can al3o have la3ting implication3 for reproductive health. Early 3exual development may lead to increased ri3k3 of reproductive health i33ue3 later in life, 3uch a3 irregular men3trual cycle3 or condition3 like polycy3tic ovary 3yndrome (PCOS) in girl3. For boy3, there can be concerns related to fertility and hormonal imbalances. Additionally, early on3et of 3exual maturity can lead to earlier initiation of 3exual activity, which may

increase the risk of unintended pregnancies and sexually transmitted infections (STIs). Comprehensive sexual education and access to appropriate healthcare services are essential to mitigate these risks.

Risk of Chronic Conditions

Research suggests that individuals with a history of precocious puberty may face an elevated risk of developing chronic health conditions later in life. Studies have indicated potential links between early maturation and conditions such as obesity, type 2 diabetes, cardiovascular disease, and certain types of cancer. The relationship between early puberty and obesity, in particular, is concerning, as the hormonal changes associated with precocious puberty can contribute to weight gain and metabolic disturbances. Furthermore, the psychosocial stressors experienced during childhood can lead to long- term mental health issues, including anxiety and depression, which are associated with various chronic health conditions.In summary, the long-term consequences of early onset puberty encompass a range of health issues that can impact growth, reproductive health, and the risk of chronic conditions. Addressing these potential outcomes through early intervention and ongoing support is essential for promoting the overall well-being of affected individuals.underlying issue.

Gonadotropin-releasing hormone (GnRH) agonists, such as leuprolide acetate, are frequently used to suppress the premature release of sex hormones. These medications work by downregulating the pituitary gland's production of luteinizing hormone (LH) and follicle-stimulating hormone (FSH), effectively pausing the progression of puberty. Treatment with GnRH agonists is generally well-tolerated, and the effects can be reversible upon discontinuation of therapy.

In cases of peripheral precocious puberty, which may be caused by conditions such as tumors or hormone-secreting lesions, treatment will focus on addressing the underlying cause. This may involve surgical intervention or medications to block the effects of excess hormones, depending on the specific diagnosis.

Diagnosis

Diagnosing precocious puberty involves:

- Reviewing the child's and the family's medical histories.
- Doing a physical exam.
- Running blood tests to measure hormone levels.

X-rays of children's hands and wrists also are helpful in diagnosing precocious puberty. These X-rays can show if the bones are growing too quickly.

development of secondary sex characteristics and early closure of epiphysis. Defining the etiologic cause is important for the management of the underlying disease. History should be sought for information about the onset of the signs, progression rate, and growth tempo in the last 6-12 months, presence of secondary sex characteristics (acne, oily skin, erection, night ejaculation and vaginal bleeding) in addition to the presence of pubertal signs. History of PP in family supports the diagnosis of familial forms. Pubertal staging should be performed according to Tanner-Marshall method on physical examination, and anthropometric evaluations should be defined by measurement of weight, height and body proportions. All old and new data should be marked on growth chart. Growth velocity per year must be calculated. If there is not any data for the past, patient should be followed prospectively for at least 6 months. Growth velocity is more than 75th percentile in most patients with CPP. Bone age should be determined by left hand and wrist X-ray. If bone age is advanced more than 2SD for chronological age it is unlikely the child has a normal variant of pubertal development If it is possible, Δ bone age/ Δ chronological age must be calculated. If this ratio is greater than , it is in favor of progressive CPP.

Finding the type of precocious puberty

A test called a gonadotropin-releasing hormone (GnRH) stimulation test helps identify the type of precocious puberty.The test involves taking a blood sample, then giving the child a shot containing the GnRH hormone. More blood samples taken over a period of time show how hormones in the child's body react.In children with central precocious puberty, the GnRH hormone causes other hormone levels to rise. In children with peripheral precocious puberty,other hormone levels stay the same. Other tests for central precocious puberty

- MRI of the brain. This imaging exam can show if children who have central precocious puberty have brain issues that are causing the early start of puberty.
- Thyroid testing. This test can show if the thyroid gland isn't making enough thyroid hormone — a condition called hypothyroidism. The test might be used with children who have symptoms of hypothyroidism, such as being tired, reacting to cold, starting to do poorly in school or having pale, dry skin.[13]

Other tests for peripheral precocious puberty Children with peripheral precocious puberty need more testing to find the cause of their condition. This might include more blood tests to check hormone levels or, in girls, an ultrasound to check for an ovarian cyst or tumor.

More information

Treatment

The primary goal of treatment is for children to grow to adult height.Treatment for precocious puberty depends on the cause. However, when no cause can be found, treatment may not be needed, depending on the child's age and how fast puberty is moving. Watching the child for several months might be an option.[14]

Treating central precocious puberty

This usually involves medicine called GnRH analogue therapy, which delays further development. It may be a monthly shot with medicine such as leuprolide acetate (Lupron Depot), or triptorelin (Trelstar, Trip to dur Kit). Or some newer formulations can be given at longer intervals. Children keep getting this medicine until they reach the usual age of puberty. After the treatment stops, puberty starts again. Another treatment option for central precocious puberty is a histerlin implant, which lasts up to a year. This treatment doesn't involve monthly shots. But it does involve minor surgery to put the implant under the skin of the upper arm. After a year, the implant is removed. If needed, a new implant.

Need for Brain MRI

Once a diagnosis of CPP has been made, clinicians are faced with the decision of whether to order a brain MRI. This decision only pertains to girls, because the much higher rate of intracranial pathology mandates central nervous system (CNS) imaging in all boys with CPP. It has been suggested that brain MRI scanning may not be necessary in girls older than age 6 years who have no neurologic symptoms . However, others have advocated for routine brain MRIs regardless of age, because of the finding of CNS abnormalities in girls with CPP who are older than age 6 years . Potential consequences of unnecessary MRIs include cost, parental anxiety, and need for repeated imaging when incidental findings are uncovered. A meta-analysis of MRI findings in children with CPP revealed a total prevalence of CNS lesions of 9%, which decreased to 7% when only those possibility related to early puberty were included . Notably, however, only 1.6% of these required intervention, because the vast majority were hypothalamic hamartomas which respond to medical therapy. Given that a Small risk of important CNS abnormalities does exist, it is unlikely that the controversy surrounding this aspect of management will be resolved any time soon. For now, the recommendation is to discuss the pros and cons of MRI scanning with parents and allow them to participate in the decision of whether or not to pursue this test.In children with a family history of CPP, genetic testing for an MKRN3 mutation, the most common monogenetic cause of precocious puberty, will likely supersede CNS imaging, rendering this issue moot in many cases . A second genetic etiology underlying familial CPP is deletions in DLK1, which encodes for Delta-Like 1 Homolog .

Both MKRN3 and DLK1 are maternally imprinted genes that are expressed only from the paternal allele. Thus, a family history of CPP on the father's side should increase the index of suspicion for a mutation in one of these genes. Other genetic causes of CPP include activating mutations in kisspeptin and its receptor, KISS1R . However, each of these has been described as causing CPP in only a single patient thus far.[15]

Monitoring of Treatment

There is no systematic strategy for monitoring whether adequate suppression of the HPG axis has been achieved in children being treated for CPP . Although there is unanimity regarding the value of auxologic indices such as growth velocity, Tanner staging, and skeletal maturation, no agreement exists on the need for biochemical measures of treatment efficacy . In fact, unexpected pitfalls are sometimes encountered when assumptions are made about hormonal studies in CPP. A case in point is the use of random ultrasensitive LH concentrations, which are helpful in the diagnosis of CPP and were postulated to adequately reflect HPG-axis suppression during treatment.

Unexpectedly, random ultrasensitive LH values frequently remain in the pubertal range in children receiving GnRHa therapy that otherwise provides adequate HPG- axis suppression, and therefore these values can be misleading . Given the lack of evidence for any association between biochemical monitoring and adult height, it is reasonable to forgo any routine blood testing in children being treated for CPP. If treatment failure is suspected on clinical grounds, a GnRHa stimulation test is recommended.[16]

Discontinuation of Therapy

A final area of uncertainty in the management of CPP relates to the optimal age of discontinuation of treatment. There are essentially no studies in which age at treatment cessation has been standardized. However, cumulative evidence suggests that optimal height gains are realized when treatment is stopped at a bone age of12 years in girls and 13 years in boys. Regardless, the decision of when to halt therapy is individualized and incorporates numerous patient- specific characteristics including absolute and predicted height, chronological age, psychosocial factors,

pubertal stage, and family preferences.[17]

Gonadal Function After GnRHa Therapy

Information regarding long-term outcomes of patients treated with GnRHas with respect to gonadal function are reassuring. Unsurprisingly, the vast majority of existing data pertain only to women. Menstrual cycles are reported to be normal with respect to duration and timing, and mean ovarian volumes similar to those in the general population. There have been no perceived health consequences to offspring of mothers who were treated with GnRHas and no increased need for assisted reproductive technology. Limited follow-up in adolescent boys previously treated with a GnRHa.[18]

CONCLUSION

Precocious puberty is a condition characterized by the early onset of secondary sexual characteristics, typically before the age of 8 in girls and 9 in boys. It is categorized into two main types: central precocious puberty (CPP), which is mediated by the early activation of the hypothalamic-pituitary-gonadal (HPG) axis, and peripheral precocious puberty (PPP), which occurs independently of the HPG axis due to excess secretion of sex hormones from other sources such as adrenal glands, gonads, or exogenous influences.

The condition has multifaceted implications, including biological, psychological, and social challenges. Biologically, it may result in accelerated growth, premature bone maturation, and reduced adult height due to the early closure of growth plates.

Psychologically, children may struggle with emotional and behavioral issues stemming from early physical changes and the misalignment of their physical development with their cognitive and emotional maturity. Socially, early puberty can lead to stigmatization or inappropriate expectations from peers and adults.

Precocious puberty can have diverse etiologies, ranging from benign idiopathic causes to serious underlying conditions such as central nervous system abnormalities, congenital adrenal hyperplasia, or hormone-secreting tumor s. A comprehensive diagnostic approach, including a thorough clinical evaluation, hormonal testing, and imaging studies, is essential to identify the underlying cause. Treatment is tailored based on the etiology and the impact of the condition on the child. GnRH analog therapy is the standard treatment for CPP, effectively delaying further pubertal progression and preserving growth potential. For PPP, management focuses on addressing the underlying cause, such as hormone-secreting tumor s or adrenal disorders. In idiopathic cases, careful monitoring may suffice. The long-term prognosis of precocious puberty depends on early identification, accurate diagnosis, and effective intervention.

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