Diagnosis, Treatment, and Outcomes of Males with Central Precocious Puberty

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KEYWORDS

• Precocious puberty • Gonadotropin-releasing hormone analogue • Short stature

KEY POINTS

- Central precocious puberty (CPP) is defined by onset of centrally activated puberty in boys prior to the age of 9 year old.
- All male patients who have biochemical CPP are recommended to have a brain MRI to evaluate the hypothalamic-pituitary region for lesions. In boys with CPP, 36% to 74% will have a detectable central nervous system lesion.
- Without treatment to halt pubertal progression, some boys with CPP will have premature closure of growth plates and reduced adult height compared to genetic potential.
- Gonadotropin-releasing hormone (GnRH) agonist treatment can halt CPP. These medications can be delivered in intramuscular, subdermal, subcutaneous, or intranasal formulations or implants. Treatment slows growth velocity and pubertal progression and increases predicted adult height during therapy, though long-term data describing boys treated for CPP are lacking.

INTRODUCTION

The typical timing of male puberty begins between 9 and 14 years old, at an average age of 11.6 $\pm$ 0.9 years.[1] Luteinizing hormone (LH), measured via an ultrasensitive assay, acts as a surrogate marker for gonadotropin-releasing hormone (GnRH) in serum laboratory studies. Central precocious puberty (CPP) is caused by a release of inhibition on pulsatile GnRH secretion.[2] Onset of puberty in boys is documented by a random LH level $\geq$ 0.3 IU/L or a peak LH > 5 IU/L after GnRH agonist (GnRHa) stimulation testing (subcutaneous leuprolide, 10 ug/kg)[3] with an increase in testicular

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volume >3 mL. Pulsatile LH stimulates Leydig cells to produce testosterone. These findings prior to the age of 9 year old are consistent with CPP .[2]

INCIDENCE AND SECULAR TRENDS

The estimated incidence of CPP ranges from 0.01 to 2/10,000 children in boys, which is less frequent than in girls (CPP rates of 0.1–26.3/10,000).[4] Unlike female puberty, which has trended to become earlier over the past 3 decades, studies in boys in different regions have had conflicting findings. While Korean and Turkish studies suggest increasing rates of CPP in boys,[4] a US study from 2001 to 2010 did not show a change in frequency of CPP in males.[5] Possible causes for the discordance between timing of onset may be definitions, visual inspection versus physical examination, laboratory verification of LH levels, and type of study performed.[6] This is an area that requires further exploration.

UNDERLYING CAUSES

Genetics, adiposity, nutritional status, environmental and chemical exposures, and chronic illnesses can impact pubertal timing in girls. However, there is limited evidence to link these to the development of CPP in males.[7] A Danish study (846 boys) examined the relationship between timing of puberty in parents and sons and found early pubertal timing of parents was associated with earlier pubertal onset in sons compared to boys with average or late maturing parents.[6] A 2022 multi-center cohort study examined the transition into puberty in adolescents born between 2003 to 2011 (68,571 boys), using age at transition from Tanner stage 1 to Tanner stage 2+ as a primary outcome.[8] Boys with overweight or obese body mass index (BMI) had earlier gonadarche compared with boys with BMI in the normal range. Underweight boys had a decreased likelihood of earlier gonadarche.[8] These findings contrast with the outcomes of prior studies, which have shown an inverse relationship between elevated BMI z-scores and age of onset of pubertal development.[9] A 2016 study found an association between earlier puberty in overweight boys and later pubertal onset in obese White non-Hispanic adolescent boys.[10]

Environmental pollutants can act as endocrine disrupting chemicals. Compounds investigated for a role in impacting pubertal timing include phthalates, bisphenol A, polychlorinated biphenyls (PCBs), perfluorooctanesulfonic acid (PFOS), and organochlorine pesticides.[11] Evidence that links exposure to alterations in timing in male puberty is limited. Some studies have shown delayed male puberty in PCB-exposed and PFOS-exposed boys,[11] and further research is needed in this area.

Primary underlying causes of CPP in males are predominantly due to central nervous system (CNS) lesions and genetic conditions, while idiopathic causes account for 10% of cases.[12] CPP is more often due to an underlying cause in males, whereas idiopathic CPP is the most common finding in girls.[4] CNS lesions associated with CPP include hypothalamic hamartomas, germ cell tumors, glial cell tumors, craniopharyngioma, and pinealomas, though any CNS lesion can be associated with CPP. Congenital brain defects such as midline anomalies, cranial irradiation, history of infection, or trauma can also be associated with CPP. Underlying genetic conditions, including neurofibromatosis-1 and tuberous sclerosis, can be risk factors for developing CPP.[2,4] (**Table 1**).

Genetic Mutations

Genetic mutations have been identified as causes of familial CPP. The most common genetic cause of CPP is loss of function mutations of the Makorin ring finger protein-3 gene (*MKRN3*). Due to the maternal imprinting inheritance pattern, CPP only occurs if

Table 1
Underlying causes of male central precocious puberty[2,4]

Category	Condition	Comments
Central nervous system Lesions	Hypothalamic hamartoma	
	Glial cell tumors	
	Germ cell tumors	
	Craniopharyngioma	
	Pinealoma	
Congenital Brain Defects	Subarachnoid cyst	
	Arachnoidocele	
	Rathke cleft cyst	
Congenital Midline Anomalies	Hydrocephalus	
	Meningomyelocele	
	Optic nerve hypoplasia	
Non-Organic Causes	Cranial irradiation	
	Previous meningoencephalitis	
	Head trauma	
	Perinatal insult	
Underlying condition	Neurofibromatosis, type 1	
	Tuberous sclerosis	
	Untreated peripheral precocious puberty (CAH, exogenous testosterone exposure)	Activation of CP due to sex steroid exposure, known as secondary CPP
	Van Wyk–Grumbach syndrome	Longstanding untreated hypothyroidism, possibly caused by elevated TRH stimulating follicle stimulating hormone(FSH)/ Luteinizing hormone (LH) secretion
	Sturge–Weber syndrome	
	Williams–Beuren syndrome	
	Temple syndrome	
	RASopathies	
Genetic Mutations	*KISS1*	Gain of function mutation
	KISS1R	Gain of function mutation in the KISS1 receptor gene
	LIN28B	Mechanism unknown
	DLK1	Gain of function mutation
	MKRN3	Gain of function mutation
	Chromosomal microdeletion (1p36, 9p)	
Idiopathic/Other	Associated with being adopted from abroad	
	Ectopic neurohypophysis	

Abbreviations: CAH, congenital adrenal hyperplasia; CP, central puberty; TRH, thyrotropin-releasing hormone.

the mutated allele is inherited from the father. In mouse models, the function of *MKRN3* is primarily to inhibit pubertal initiation. One meta-analysis described *MKRN3* defects in 13 boys.[13] The boys experiencing CPP associated with a *MKRN3* defect had later onset of puberty compared to boys experiencing CPP without a *MKRN3* defect (8.2 vs 7 years, respectively).[14] The gene delta-like non-canonical notch ligand-1 (*DLK1*) is a paternally expressed transmembrane protein present in a variety of embryonic tissues. Defects in this gene are associated with higher risk of obesity, diabetes mellitus, and CPP.[15] In 2022, the first male patient with CPP due to a *DLK1* gene mutation was identified. His sister and father were also affected.[16] Mutations in genes associated with kisspeptin (*KISS1*) or its receptor (*KISS1R*) also cause CPP. Kisspeptin neurons are involved in pulsatile GnRH release, leading to onset of central puberty.[17] A heterozygous mutation (p.P74S) in *KISS1* was identified in a boy with sporadic CPP at age 12 months.[18]

Among the less common gene mutations associated with CPP, only a mutation in *NOTCH1* has been associated with a case of male CPP, and the rest have only been described in females.[19]

CLINICAL EVALUATION AND DIAGNOSIS

Boys with CPP typically have symmetric, pubertal sized (>3 cc) testes on examination. The presence of pubertal symptoms with pre-pubertal testes (volume $\leq$ 3 cc) indicates that androgens are being produced elsewhere, as is seen with premature adrenarche (a benign variant) or are from an adrenal or exogenous source (examples include congenital adrenal hyperplasia [CAH], adrenal tumors, and exogenous testosterone exposure). Asymmetric testicular volumes are not consistent with stimulation by circulating gonadotropins in CPP, and may indicate a peripheral source of androgens such as a testicular tumor.[7] Asymmetry may also result from earlier testicular damage or correction of cryptorchidism after infancy.

After determining that a male patient less than 9 year old has symmetrically enlarged (>3 cc) testes, the next step in evaluation is measurement of serum gonadotropins (follicle stimulating hormone[FSH]/luteinizing hormone [LH]) and total testosterone levels, which are typically elevated. Serum gonadotropin levels monitored by ultrasensitive assays are preferred and ideally obtained in the morning due to the pulsatile release and higher amplitude of gonadotropin action in the early morning during the initial stages of puberty.[4,12] Human chorionic gonadotropin (hCG) is also measured to rule out pathologic elevation which can occur in the setting of certain tumors.

If, despite low or pre-pubertal gonadotropin levels, there remains a high level of clinical suspicion for CPP, a GnRH stimulation test is the next step in evaluation, as described in (see Kanthi Bangalore Krishna and Lawrence A. Silverman's article, "Diagnosis of Central Precocious Puberty," in this issue). Measurement of pubertal levels of LH after GnRH stimulation indicates that endogenous GnRH exposure has "primed" the pituitary gonadotrophs.[20] The laboratory findings most typical in CPP include pubertal unstimulated gonadotropin levels or elevated gonadotropins after GnRH stimulation testing, undetectable serum hCG, and elevated serum testosterone levels.

Once CPP is identified, the next step is to evaluate if there is an underlying cause (see **Table 1**) and to assess the tempo of pubertal progression. A bone age (BA) significantly advanced for chronologic age indicates greater exposure to sex steroids. If the BA is consistent with chronologic age, then it is less likely that the patient has had significant exposure to high concentrations of sex steroids.[2]

All male patients who have biochemical CPP require a brain MRI with contrast to evaluate the hypothalamic-pituitary region for lesions. In contrast to girls, who are

likely to have idiopathic CPP, boys are more likely (36%–74% in various studies) to have a CNS lesion associated with CPP.[4,5]

TREATMENT

Decisions surrounding treatment initiation should consider underlying etiology, family history, height prediction, and tempo of pubertal progression. In patients with a strong family history of onset within the early range, but not central precocious puberty, with rapid advancement of physical development, this variation of normal may require treatment. In the absence of rapid pubertal progression or psychosocial distress, a 3-to-6-month period of observation can be considered prior to initiation of treatment.[20] Goals of treatment in males are (1) halt further development of secondary sexual characteristics, (2) prevent psychological disturbance, and (3) preserve final adult height (FAH).[20,21] However, criteria to identify patients who require treatment have not been established. Overall, the strongest indications for treatment are among younger patients, in those with BA advancement of more than 2 years beyond chronologic age, and in those with predicted adult height less than 165 cm or greater than 5 cm below mid-parental height.[20–22]

GnRHa are used to halt pubertal progression in boys with CPP through tonic GnRH action at the receptor, overriding the endogenous pulsatile release pattern that stimulates gonadotropins. The consistent presence of GnRH transiently leads to stimulation of GnRH receptors, followed by a downregulation of GnRH receptors on the pituitary. This downregulation causes decreased sensitivity to GnRH and reduction in release of gonadotropins, which halts stimulation of the testes to produce testosterone. Available GnRHa formulations are described in **Table 2**. Specific guidelines about discontinuation of GnRHa in boys do not currently exist, but typically therapy is continued until approximately age 12 years.[20,21]

Clinical evaluation is used to assess response to pubertal suppression with GnRHa and should be completed every 3 to 6 months with measurement of growth velocity (GV) and Tanner staging. BA can be monitored periodically, with an expectation that the rate of BA advancement slows by a year after beginning GnRHa therapy.[20] To assess biochemical efficacy, serum LH levels can be measured prior to a GnRHa dose, with a goal of LH in the pre-pubertal range. In patients with a histrelin implant, LH levels may not be suppressed in approximately 60% of cases, so clinical assessment is the most effective way to assess efficacy of treatment.[20,23]

When GnRHa therapy is discontinued, the hypothalamic–pituitary–gonadal (HPG) axis typically shows signs of reactivation well before 12 months. The most common short-term side effect associated with leuprolide is sterile abscess at injection sites.[20,21]

Various formulations of GnRHa treatment for CPP have been evaluated. Study cohorts mainly include girls due to their higher frequency of CPP. As a result, there is

Table 2
Currently available formulations of gonadotropin-releasing hormone analogs[27,28]

Drug Name	Route of Administration	Frequency of Administration
Leuprolide acetate depot	IM, SQ injection	1-mo, 3-mo, or 6-mo formulations
Histrelin	Subdermal implant	1–2 y
Triptorelin	IM injection	1-mo, 3-mo, or 6-mo formulations
Nafarelin acetate (rarely used)	Intranasal	Every 12 h
Leuprolide acetate (rarely used)	Subcutaneous injection	Daily

limited information about these medications in male patients, and specific outcomes in the male patients were not reported in the studies. A study on the 3-month formulation of triptorelin (11.25 mg) demonstrated adequate LH suppression at 3, 6, and 12 months after treatment initiation in 4 out of 5 boys.[24] Two studies of the 3-month formulations of leuprolide acetate (11.25 mg, 30 mg) included 7 and 8 boys, respectively, and a study utilizing the 6-month (45 mg) formulation included 2 boys.[25–27] Both 3-month formulations (11.25 and 30 mg) and the 6-month (45 mg) formulation preparations were effective at suppressing pubertal progression after 6 months of use.[25–27] A study of the 6-month formulation of triptorelin, which included 9 boys, reported effective suppression of gonadotropins and improved predicted adult height (PAH) during the treatment course.[28]

OUTCOMES OF TREATED AND UNTREATED CENTRAL PRECOCIOUS PUBERTY IN MALES

Due to the rare incidence of idiopathic CPP in boys, limited data regarding treatment outcomes in males are available. **Table 3** summarizes previous unreported outcome data for 3 men now in their 40s. For the 2 men who did not have a pre-existing condition, their outcome was excellent, including social interactions, work, family relationships, and fertility, while treatment was begun so late that they had compromised adult heights. Published outcome information is included in the following paragraphs according to topics.

Growth Velocity and Final Adult Height

Without treatment to halt pubertal progression, some boys with CPP will have reduced adult height, up to 3 standard deviations below normal values for matched peers.[22] An analysis of adult height in 9 boys (age 6.0 $\pm$ 1.8 years at therapy initiation) with CPP treated with GnRHa therapy (duration 5.6 $\pm$ 2.4 years) found final adult height (FAH) to be significantly higher than the initial predicted adult height (PAH) at time of evaluation, and within range for mid parental height. The outcomes did not differ based upon type or duration of GnRH analog used or underlying cause of CPP.[29] A study of 23 boys treated for CPP with GnRHa therapy showed improved PAH after 12 months of therapy compared to baseline predictions. They also found that after 12 months of therapy, GV decreased from baseline, suggesting a decline in growth acceleration, with the expectation that growth plate maturation would also slow and allow more time for linear growth.[30] FAH was not reported in this study. Multiple other studies have showed slowed GV during GnRHa treatment and increased PAH during therapy.[31–33] A retrospective study of 18 boys with CPP who were evaluated prior to GnRHa treatment, 1 year into GnRH treatment, and once FAH was reached showed that FAH was consistent with and slightly greater than mid-parental height (172.0 $\pm$ 4.8 cm vs 171.4 $\pm$ 4.0 cm respectively). These results support improved growth potential with GnRHa treatment.[33,34] Studies have shown that growth after cessation of GnRHa therapy is correlated with BA at time of discontinuation of treatment, and that discontinuation of treatment at a BA close to peak height velocity may be most beneficial to improve FAH.[22]

Augmentation of Growth in Addition to Gonadotropin-Releasing Hormone Agonist Therapy

Aromatase inhibitors (AI) have been explored as part of growth-promoting treatment for boys with short stature (idiopathic short stature, familial male-limited precocious puberty), but publications about AI use in boys with CPP are limited to case

Table 3
Previously unpublished long-term follow-up of 3 patients

		Patient 1	Patient 2	Patient 3
Age (years)	Current	47	47	41
	At diagnosis	9.4	10.2	9.8
	At therapy onset	9.5	10.7	10.8
	At end of therapy	12.4	13.3	14.5
Gonadotropin-releasing hormone agonist (GnRHa)	Daily Aqueous/1 mo. Depot	Aqueous	Aqueous	Depot
	Duration	3.0	2.8	3.7
Height (cm)	At diagnosis	145.6	148.9	156.0
	At onset of therapy	147.2	153.9	160.3
	At end of therapy	163.6	168.3	178.3
	Target height range	1.57–1.83	Adopted	1.63–1.80
	Predicted adult height (AH) onset of therapy	167.5	179.9	175.0
	PAH end of therapy	170.4	176.4	180.1
	Growth post-Rx	8.5	2.8	1.3
	Adult height	172.1	171.1	179.6
Skeletal age	At onset of therapy	13.25	14.25	13.0
	At end of therapy	13.5	14.5	17.0
Academic achievement		BA with honors, MA-full scholarship	Poor attention deficit hyperactivity disorder, Intellectual disability	College
Physical fitness		Excellent	Poor	Good
Employment		Corporate VP	Restaurant (25 y)	IT (25y)
Partner pregnancy		X3, 1–3 mo attempting	NA	Yes, first month attempting
Children	Sex and Age	Male 17 y Female 13 y Male 9 y	NA	Female 9 y
	Medical conditions	Healthy, normal puberty	NA	None
Significant medical conditions		None	Obesity post-treatment	None
Perception of GnRHa therapy benefit		Hoped to be even taller	"Probably helped"	Hoped to be even taller
Perception of impact of central precocious puberty (CPP)		Assumed that he would be taller because of height during childhood	Still unaware of the fact that his puberty was early	Bullied after being placed with older teens

(*continued on next page*)

Table 3
(continued)

	Patient 1	Patient 2	Patient 3
Comments	Remarkably well-adjusted adult. Accepts adult height. Commendable family, work, and social life.	Therapy stopped because of slow growth. Prostate massage swab showed living sperm	Wonders if erectile dysfunction started earlier due to CPP

reports.[35,36] A male with CPP with prior attempted surgery for a hamartoma not treated with GnRHa was treated with anastrozole 1 mg daily for 3 years and the patient had a gain of 6 cm compared to the initial PAH.[37]

Few studies have examined the use of growth hormone (GH) in conjunction with GnRHa therapy in children with CPP.[38] One study of 14 children (10 girls, 4 boys) who had a decline in GV to less than the 25th percentile during treatment for CPP and had no improvement in PAH were treated with GH (0.3 mg/kg/week) for 2 to 3 years. Outcomes in boys showed no significant change in GV throughout treatment but did show improvement in PAH in the first year after combined treatment. However, the change in PAH was not statistically significant, and FAH had not been achieved at the time of publication.[31,38]

Body Mass Index and Cardiovascular Effects

A retrospective study of children previously treated with GnRHa for CPP showed no significant difference in BMI from the start to end of therapy or at a time measured later when they were near FAH.[39] There was no difference in glucose or lipid values between treated patients and controls, implying GnRHa therapy had minimal effects.[39] A Portuguese study (8 boys with CPP) showed that boys were heavier than girls prior to treatment and did not have an increase in BMI z-score during treatment. Both sexes had a decreased BMI z-score from baseline to a year after ending GnRHa therapy.[40] A study of the histrelin implant found a decrease in BMI percentiles in all patients (29 girls, 2 boys) at 24 months of treatment compared to baseline, though outcomes over a longer duration were not reported.[23]

Fertility Outcomes

A limited number of studies examined long-term gonadal function in males with CPP after GnRHa treatment and reported normal gonadal function and no alteration in serum testosterone levels or semen analyses compared to males with normal pubertal timing.[29,41] One study of 14 patients (7 males) with CPP due to hypothalamic hamartoma found that at adulthood all subjects had normal gonadal function; 3 males had fathered children.[42]

Bone Mineral Density

Bone mineral mass increases throughout childhood and during puberty. Compared to pre-pubertal girls, pre-pubertal boys have slightly higher total body bone mineral content.[43] One longitudinal study of children treated with GnRHa therapy for CPP (2 boys) showed that when corrected for BA, children had normal bone mineral density (BMD) before, during, and after treatment.[44] One Italian study of 9 males treated with GnRHa therapy found that after therapy (mean age 16.7 $\pm$ 1.5 years), BMD values were within normal range and comparable to men with average onset of pubertal timing.[29]

Psychosocial Outcomes

There are limited studies assessing the psychosocial functioning of males with treated or untreated CPP. One study of caregivers of 3491 children (50.8% boys) reported that in boys with signs of puberty by age 8 to 9, there was worse psychosocial adjustment from early childhood through adolescence and increased behavioral difficulties.[45] A cross-sectional study of caregivers of patients with CPP (21 boys, 121 girls) found that children with CPP have poorer psychosocial health and emotional functioning compared to peers without CPP. Outcomes did not differ among children with CPP who had or had not undergone treatment. Results were not reported by gender.[46]

SUMMARY

CPP in males is rare, and long-term outcome studies on males with CPP are lacking. Males with CPP are more likely to have an underlying CNS cause, and therefore all boys with CPP require evaluation with brain MRI. While treatment of male CPP with GnRHa therapy leads to slowed growth velocity and increased predicted adult height, further studies need to be conducted to examine the impact of GnRHa treatment with respect to FAH, BMI, future fertility, and psychosocial outcomes.

CLINICS CARE POINTS

- The first sign of puberty in males is testicular growth; volume greater than 3 mL or longitudinal axis greater than 2.5 cm is indicative of growth.
- Central precocious puberty [early resurgence of the hypothalamic-pituitary-testicular (HPT) axis] is less common among males than females, although it is more likely to have an underlying pathologic cause. Hence, imaging studies of the CNS are done more frequently.
- GnRH analogs are the treatment of choice to halt pubertal development in males, and monitoring of therapy is simpler than among females, since suppressed testosterone levels are indicative of axis suppression.
- Limited outcome data indicate that therapy
  - preserves or reclaims growth potential depending upon degree of advancement of bone age at onset of therapy.
  - The HPT axis is active within months of stopping therapy.
- Available long-term outcome data indicate that quality of life (social, sexual, work, fertility) is normal among males after CPP and GnRHa therapy.

DISCLOSURE

The authors have no conflicts of interest to disclose.

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