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Review

Adult Height in Girls with Idiopathic Central Precocious Puberty

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Abstract: Precocious puberty (PP) is characterized by the early onset of secondary sexual characteristics and accelerated growth, which often result in compromised adult height (AH). Central precocious puberty (CPP), a subset of PP, is treated with gonadotropin-releasing hormone analogs (GnRHa) to suppress premature hormonal activation and delay epiphyseal closure, thereby preserving height potential. The present review examined the effects of GnRHa on AH outcomes in girls with idiopathic CPP. Although AH is greater with GnRHa therapy than without it, the treatment does not consistently restore the patient's genetic potential. The benefits of the treatment are most evident in girls in whom idiopathic CPP is diagnosed before 6 years of age and they achieve a height gain of 4.5–14.1 cm, which is unattainable without treatment. However, the treatment of older children (ages 6–8) shows conflicting results, with the AH outcome varying among previous reports. In particular, slowly progressive CPP is known to have a favorable height prognosis even without treatment. Another factor influencing the AH prognosis is the timing of GnRHa discontinuation; the best time to discontinue GnRHa therapy for the best AH outcome is reportedly the bone age of approximately 12 years. In conclusion, although GnRHa therapy significantly improves the AH, especially in early-onset CPP, its effectiveness is uncertain in borderline or late-onset cases. Further research is required to formulate more precise criteria for patient selection and treatment discontinuation to optimize the height outcome in girls with idiopathic CPP.

Keywords: central precocious puberty; adult height; gonadotropin-releasing hormone analogs

Introduction

Recent studies have highlighted a global trend toward earlier pubertal onset in girls, as measured by the onset of breast development. Camilla *et al.* [1] reported in a systematic review and meta-analysis that the age at thelarche decreased by an average of three months per decade from 1977 to 2013. This trend may also have increased the number of patients with precocious puberty (PP), the definition of which has not been revised for several decades.

PP is a condition in which the secretion of sex hormones is enhanced at an early chronological age (CA), resulting in the earlier appearance of physical, pubertal changes, such as breast development. PP is classified into a gonadotropin-dependent form, referred to as central PP (CPP) in this manuscript, and a gonadotropin-independent form. These two types are caused by the central activation of the hypothalamus and pituitary gland and by other mechanisms related to peripheral gonadal and adrenal gland tumors, respectively. CPP is more common in girls, with 70-80% of cases being idiopathic. In boys, 25% of cases are idiopathic, with the rest being organic [2].

The clinical problems associated with PP include 1) serious complications, such as a brain tumor or sex hormone-producing tumor; 2) psychological and social problems due to the early appearance and progression of secondary sexual characteristics; and 3) compromised adult height (AH) due to

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early growth arrest. In PP, excess sex hormones increase the growth rate at the initial presentation but also accelerate bone maturation, causing early growth plate closure.

In children with CPP, gonadotropin-releasing hormone analogs (GnRHa) have been the treatment of choice for nearly 40 years [3]. Although this therapy is beneficial (see below), uncertainty regarding its ability to achieve the desired AH remains [4,5]. For example, randomized controlled trials have not been conducted, and the comparisons of historical controls and treatment groups between 1990 and 2007 included only small numbers of heterogeneous patients [3]. The present review examines the effects of GnRHa therapy on the AH of girls with idiopathic CPP.

Adult Height of Patients with Idiopathic Central Precocious Puberty Receiving GnRHa

Table 1 shows 24 reports of AH outcomes in female patients with idiopathic CPP receiving GnRHa therapy [6–29]. The age range at puberty onset was 3–8 years. Young children in past studies were diagnosed with a severe form of CPP whereas older patients in more recent studies who began therapy at the age of 5.4–8.9 years had a milder form. The mean bone age (BA) of patients with idiopathic CPP (Table 1) at the start of treatment was approximately 10 years (range: 8.2–11.1 years), and the mean duration of treatment was approximately 3.0 years. In all but two reports [27,29], AH was 1.1-10.5 cm greater than the predicted adult height (PAH). However, AH was 0.1–7.1 cm below the target height (TH) in 16 reports [6,7,9,10,12,14–19,21,22,24,26,29] but was 0.4–3.6 cm above the TH in the remaining eight studies [8,11,13,20,23,25,27,28], indicating that GnRHa therapy may not be sufficient for the patient to attain their genetic height potential.

Table 2 shows that AH differed by the age at treatment initiation. Girls with idiopathic CPP who were younger than 6 years achieved an average AH increase of 9 to 10 cm although there was significant variation [6,14,15,30,31]. Similarly, Carel *et al.* [11] reported that AH increased 4.5–5.3 cm above the pretreatment PAH in 42 treated girls who had puberty onset at the age of 6–8 years. Similarly, Lazer *et al.* demonstrated that AH increased 7.2 ± 5.3 cm in girls who were aged ≥ 6 years old and had already begun puberty [30]. Klein *et al.*[15] also found that the age of 6 years or older was associated with the best treatment outcome: the mean AH of the girls who began treatment at the age of 6–8 years was significantly greater (6.8 ± 6.9 cm) than their pretreatment PAH.

In contrast, Kletter *et al.* [6]. reviewed the AH of 131 girls treated in ten different clinical study groups and concluded that the treatment did not improve AH in girls aged > 6 years at diagnosis. This conclusion was based on the finding that the AH of 114 girls aged ≥ 6 years did not differ from that of 54 controls. The reason for the difference in growth outcomes in these patients may be explained by the lack of homogeneity in the sample population. The data given above indicate that the decision to begin treatment should be individualized for girls in whom the disease develops after the age of 6 years.

Few studies have compared treated and untreated patients with idiopathic CPP. Table 3 summarizes the comparative data on treated and untreated groups published thus far. The untreated groups mostly comprised patients who came to hospital at more advanced pubertal stages and did not receive treatment; they were not enrolled in a randomized trial. Paul et al.'s [32] comparison of three sets of data on treated and untreated girls with idiopathic CPP [33–35] found that the median age at treatment initiation was 4.7 years and that the average AH was 7.8 cm greater for treated (160.5±6.6 cm) than for untreated (152.7 ± 8.6 cm) patients. Although the mean AH of the treated patients was one standard deviation (SD) less than the TH, this outcome was superior to the mean AH of the untreated patients, which was -2.4 SD below the TH.

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Table 1. Adult height of girls with idiopathic central precocious puberty receiving GnRHa therapy.

	n	CA at diagnosis (years)	BA at diagnosis (years)	CA at end of treatment (years)	TH (cm) (SDS)	PAH (cm) (SDS)	AH (cm) (SDS)	AH-TH (cm)	AH-PAH (cm)
Kletter et al, 1994 [6]	131	7.6 ± 0.13	10.9 ± 0.1	n/a	161.8 ± 0.7	155.9	157.9 ± 0.6	-3.9	2.0
Oostdijk et al, 1996 [7]	31	7.7	10.8	11.1	168.7 ± 6.4	158.2 ± 7.4	161.6 ± 7.0 (-1.08)	-7.1	3.4
Kauli et al, 1997 [8]	48	8.3± 1.5	12.5± 0.7	11.5± 0.5	157.7± 5.7	156.6± 6.7	159.6 ± 6.3	1.9	3.0
Bertelloni et al, 1998 [9]	14	6.2 ± 1.8	9.6 ± 1.6	n/a	163.3 ± 6.2	153.5 ± 7.2	158.1 ± 5.2	-5.2	4.6
Arrigo et al, 1999 [10]	71	7.0 ± 1.3	9.8 ± 1.4	11.0 ± 1.0	161.5 ± 6.9	155.5 ± 7.0	158.4 ± 5.8	-2.9	2.9
Carel et al, 1999 [11]	58	7.5 ± 1.4	10.1 ± 1.5	11.2 ± 1.0	160.1 ± 4.4	156.4 ± 6.3	161.1 ± 5.9 (-2.5 ± 1.7)	1.0	4.7
Heger et al, 1999 [12]	50	6.2 ± 2.0	9.3 ± 2.5	11.0 ± 1.1	163.6 ± 6.2 (-0.7 ± 1.2)	154.9 ± 9.6 (-2.4 ± 1.9)	160.5 ± 8.0 (-1.3 ± 1.6)	-2.0	5.7
Léger et al, 2000 [13]	9	8.7 ± 0.4	11.1 ± 0.4	10.8 ± 0.6	159.8 ± 4.6	155.3 ± 5.6	160.2 ± 6.7	0.4	4.9
Partsch et al, 2000 [14]	52	6.2 ± 0.3	9.3 ± 0.3	11.1 ± 1.1	164	154.9 ± 9.6	160.6 ± 8.0	-3.4	5.7
Klein et al, 2001 [15]	80	5.4 ± 1.9	10.0 ± 2.7	11.1 ± 1.0	163.7 ± 5.6	149.3 ± 9.6 (2.8 ± 1.2)	159.8 ± 7.6 (-0.6 ± 1.2)	-3.9	10.5
Adan et al, 2002 [16]	43	7.9 ± 1.3	10.3 ± 1.3	10.8 ± 0.7	161.2 ± 0.7	156 ± 1.2	159 ± 5.3	-1.7	3.5
Bajpai et al, 2002 [17]	30	6.5 ± 1.8	10.1 ± 1.6	10.2 ± 2.5	154.7 ± 6.1	143.4 ±8.3	149.8 ± 6.9	-4.9	6.4
Tanaka et al, 2005 [18]	63	7.7 ± 2.2	10.2 ± 1.5	11.6 ± 1.4	154.9 ± 4.6 (-0.61±0.91)	151.1 ± 7.3	154.5 ± 5.7 (-0.67±1.13)	-0.1	3.4
Brito et al, 2008 [19]	45	7.3 ± 2.0	10.6 ± 2.2	10.7 ± 0.8	157.5 ± 4.5 (-0.8 ± 0.7)	151.5 ± 9.7	155.3 ± 6.9 (-1.2±1)	-2.2	3.7
Pasquino et al, 2008[20]	87	8.4 ± 1.5	11.1 ± 1.6	12.6 ± 1.0	157.6 ± 4.7	154.2 ± 5.2	159.8 ± 5.3	2.2	5.6
Nabhan et al, 2008 [21]	26	7.2 ± 2.0	10.1 ± 2.2	10.9 ± 1.2	164.0 ± 5.7	158.5 ± 6.8	163 ± 7.6	-1.0	4.5
Lee et al, 2011 [22]	29	7.3 ± 1.9	10.2 ± 2.1	n/a	163.8	157.4	162.5	-1.3	5.1
Poomthavorn et al, 2011 [23]	47	8.5 ± 1.0	11.1 ± 1.7	11.8 ± 1.0	155.8 ± 4.1	155.3 ± 6.7	158.6 ± 5.2	2.8	3.3
Gillis et al, 2013 [24]	23	8.4 ± 0.3	10.4 ± 0.4	11.7	160.8 ± 0.8 (-0.5±0.13)	155.2 ± 1.9	157.9 ± 1.7	-0.9	2.7
Jung et al, 2014 [25]	59	8.7 ± 0.8	10.2 ± 1.6	10.6 ± 0.8	159.9 ± 3.5	156.6 ± 4.0	160.4 ± 4.2	0.5	3.8
Bertelloni et al, 2015 [26]	12	7.9 ± 0.6	10.6 ± 0.9	n/a	159.7 ± 3.8	155.0 ± 3.5	157.1 ± 4.9	-2.6	2.1
Liang et al, 2015 [27]	17	8.1 ± 0.2	9.2 ± 0.3	n/a	158.3 ± 0.9	161.6 ± 0.9	159.8 ± 1.2	1.5	-1.8
Lin et al, 2017 [28]	87	8.9 ± 1.2	10.6 ± 0.7	n/a	157.3 ± 3.7	159.8 ± 7.1	160.0 ± 5.4	3.6	1.1
Knific et al, 2022 [29]	48	7.3 ± 1.8	8.2 ± 1.9 (1.97)	10.1 ± 0.9	164.8 ± 7.0 (-0.34)	162.7 ± 5.6 (0.17)	171.5 ± 7.5 (-0.38)	-1.4 (-0.24)	-3.5 (-0.56)

BA, bone age; CA, chronological age; TH, target height; PAH, predicted adult height; AH, adult height; n/a, not available. Data are expressed as the mean ± standard deviation.

Table 2. Adult height by age at treatment initiation in girls with idiopathic central precocious puberty.

	n	CA at diagnosis (years)		TH (cm)	PAH (cm)	AH (cm)	AH-TH (cm)	AH-PAH (cm)
Kletter et al, 1994 [6]	131	7.6 ± 0.13		161.8 ± 0.7	155.9	157.9 ± 0.6	-3.9	2.0
	17	< 6 years	4.7 ± 0.3	164.5 ± 1.4	n/a	160.4 ± 1.8	-4.1	n/a
	114	> 6 years	8.1 ± 0.1	161.4 ± 0.6	n/a	157.5 ± 0.6	-3.9	n/a

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Partsch et al, 2000 [14]	52	6.2 ± 0.3		164	154.9 ± 9.6	160.6 ± 8.0	-3.4	5.7
		< 6 years	5.0 ± 0.35	162.4 ± 1.1	152.1 ± 2.2	161.6 ± 1.43	-0.8	9.6
		> 6 years	7.8 ± 0.18	165.3 ± 1.4	157.7 ± 1.8	159.4 ± 1.75	-5.9	1.7
Klein et al, 2001 [15]	80	5.4 ± 1.9		163.7 ± 5.6	149.3 ± 9.6	159.8 ± 7.6	-3.9	10.5
		< 6 years	n/a	164.5 ± 5.9	n/a	162.1 ± 7.0	-2.4	14.5
		> 6 years	n/a	n/a	151.1 ± 8.6	157.9 ± 7.6	n/a	6.8
Lazar et al, 2007 [30]	60	< 6 years	6.4 ± 1.2	159.3 ± 5.0	154.6 ± 6.6	162.8 ± 5.0	3.1	8.2
		> 6 years	7.5 ± 0.6	157.8 ± 5.2	153.7 ± 6.7	157.9 ± 5.1	4.2	0.1
Vuralli et al, 2020 [31]	23	< 6 years	5.4 ± 0.6	-0.7 ± 0.9 (SD)	-2.6 ± 1.1 (SD)	-0.6 ± 0.8 (SD)	0.6 (SD)	2.0 (SD)
	45	> 6 years	6.5 ± 0.9	-0.9 ± 0.7 (SD)	-1.7 ± 0.8 (SD)	-0.7 ± 0.9 (SD)	0.2 (SD)	1.0 (SD)

CA, chronological age; TH, target height; PAH, predicted adult height; AH, adult height; n/a, not available. Data are expressed as the mean ± standard deviation.

Table 3. Adult height of treated and untreated girls with idiopathic central precocious puberty

		n	CA at diagnosis (years)	TH (cm)	PAH (cm)	AH (cm)	AH-TH (cm)	AH-PAH (cm)
Paul et al, 1995 [32]	Treated	26	n/a	n/a	n/a	160.5 ± 6.6	-1.0 SD	n/a
	Untreated	116	n/a	n/a	n/a	152.7 ± 8.6	-2.4 SD	n/a
Kauli et al, 1997 [8]	Treated	48	8.3 ± 1.5	157.7 ± 5.7	156.6 ± 6.7	159.6 ± 6.3	1.9	3.0
	Untreated	28	7.8 ± 1.0	159.3 ± 6.1	n/a	155.5 ± 7.5	-3.8	n/a
Carel et al, 1999 [11]	Treated	58	6.3 ± 1.6	160.1 ± 4.4	156.4 ± 6.3	161.1 ± 5.9	1.0	5.1
	Untreated	86	5.3 ± 1.9	n/a	n/a	152.3 ± 7.6	n/a	n/a
Cassio et al, 1999 [46]	Treated	20	8.5 ± 0.6	157.0 ± 5.2	n/a	158.1 ± 6.2	1.1	n/a
	Untreated	18	8.4 ± 0.5	158.5 ± 4.2	n/a	158.6 ± 6.0	0.1	n/a
Antoniazzi et al, 2002 [36]	Treated	15	9.8 ± 1.0	157.6 ± 5.9	n/a	160.6 ± 5.7	n/a	n/a
	Untreated	10	9.6 ± 2.2	156.4 ± 1.3	n/a	149.6 ± 6.3	3.0	n/a
Magiakou et al, 2010 [37]	Treated	33	7.9	158.8	158.2	158.5	-0.3	0.4
	Untreated	14	7.95	161.2	160.2	161.5	0.3	1.5
Vuralli et al, 2020 [31]	Treated	23	≦6.4 years 5.2 ± 0.6	-0.7 ± 0.9*	-2.6 ± 1.1*	-0.6 ± 0.8*	0.6 ± 0.6*	-0.6 ± 0.8*
		45	6.4–8.3 years 6.5 ± 0.9	-0.9 ± 0.7* -0.8 ± 0.6*	-1.7 ± 0.8* -1.6 ± 0.7*	-0.7 ± 0.9* -1.0 ± 0.7*	0.2 ± 0.8* -0.5 ± 0.4*	-0.7 ± 0.9* -1.0 ± 0.7*
		15	≧ 8.3 years 7.8 ± 0.5					
	Untreated	18	7.5 ± 0.8	-0.6 ± 0.7*	-1.5 ± 0.9*	-0.9 ± 1.0*	-0.3 ± 0.7*	0.7 ± 0.6*

CA, chronological age; TH, target height; PAH, predicted adult height; AH, adult height

Kauli *et al.* [8], Carel *et al* [11]., and Antoniazzi *et al.* [36] reported that AH was greater than the TH in treated patients; the mean AH of the untreated patients fell short of the TH. Magiakou *et al.* [37] compared girls who reached puberty at the age of 7.9 years with untreated patients, both of whom achieved an AH close to the TH. A recently published retrospective study [38] of girls with idiopathic CPP onset at the age of 6, 7 or 8 years revealed that GnRHa therapy improved adult height (AH) as compared to the TH although this data may have included those of slowly progressive PP (see below). Their next analysis in the same paper has overcome this issue by including a pair of patients matched for age at onset in the treated and untreated groups [38]. Future comparisons should be made within a group that excludes patients with slowly progressive PP.

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Adult Height in Patients with Slowly Progressive Central Precocious Puberty

Table 4 shows the definition of slowly progressive CPP in girls used in this review. These criteria, which aim to distinguish (idiopathic) progressive CPP from slowly progressive CPP, were formulated using data from past, cross-sectional and small, longitudinal studies [2,15,39,40].

Patients with slowly progressive CPP do not necessarily have a poor AH outcome even without treatment. The progression of hormonal activation in this type of CPP is somewhat slower in girls, as the luteinizing hormone concentration falls within the prepubertal or early puberty range at the initial presentation, indicating that the hypothalamic-pituitary-gonadal axis is not fully active. Some studies of GnRH stimulation in this population have found a predominantly follicle-stimulating hormone response [8,9,39]. The BA of these patients is not very advanced at the initial diagnosis, which probably accounts for the good AH (as discussed below) despite the early onset of secondary sexual characteristics.

Table 4. Comparison of girls with progressive and slowly progressive idiopathic central precocious puberty.

Criterion	Progressive precocious puberty	Slowly progressive precocious puberty (referred to as slowly progressive central precocious puberty)
Clinical		
Progression through pubertal stages	Progression from one stage to the next in 3–6 mo	Stabilization or regression of pubertal signs
Growth velocity	Accelerated (> about 6 cm per year)	Usually normal for age
Bone age advancement	Usually advanced by at least 1 year	Usually within 1 year of chronological age
Predicted adult height	Below target height range or declining in serial determinations	Within target height range
Hormone level		
Estradiol	Usually measurable estradiol level with advancing pubertal development	Estradiol not detectable or close to the detection limit
LH peak after GnRH	In the pubertal range	In the pubertal range

GnRH, gonadotropin-releasing hormone; LH, luteinizing hormone

Table 5 summarizes the previous studies which reported a difference ranging from −2.8 cm to 1.5 cm between AH and the TH in girls with slowly progressive idiopathic CPP. On average, AH was 0.65 cm lower than the TH [6,13,29,37,39,41–43]. Carel *et al.* recommended a follow-up examination every three to six months without therapy to assess the rate of progression if the clinical course suggests slowly progressive PP [2]. In short, this normal variant appears similar to, but actually differs from, progressive CPP, which is treatable.

In Japan, Tanaka *et al.* [44] reported in their longitudinal study that approximately 1~10% of girls (8.1~10.8%, 4.0~7.2%, 2.8~7.9%, and 1.4~4.7% at the age of 6, 7, 8, and 9 years, respectively) in one elementary school demonstrated transient breast development (n=894 in total). Many pediatric endocrinologists in Japan, including the authors of the present review, encounter similar patients in their clinical practice, suggesting that this type of transient breast development may merely be another, normal, variation in pubertal development. Although the long-term prognosis of this variant has not been studied yet, clinical experience would suggest that it has several favorable aspects compared to the other types, including its relatively light impact on the social and psychological dimensions of the patients' life as well as its superior AH outcomes.

Table 5. Adult height in untreated girls with slowly progressive idiopathic central precocious puberty

.	n	CA at diagnosis (years)	BA (years)	Menarche (age)	TH (cm)	AH (cm)	AH-TH (cm)
Brauner et al, 1994 [41]	15	7.9	9.4	10.4	161	162	1
Kletter and Kelch et al, 1994 [6]	66	7.6	10.1	n/a	161.2	161.5	0.3
Bar et al, 1995 [42]	20	5.6	8.4	10.5	163.8	161.4	-2.4

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Palmert et al, 1999 [39]	16	5.5	7.9	11	164	165.5	1.5
Leger et al, 2000 [13]	17	7.4	9.2	11.9	161.3	160.7	- 0.7
Magiakou et al, 2010 [37]	14	7.9	10.8	n/a	161.2	161.5	0.3
Allali et al, 2011[43]	52	8	9.1	n/a	159.3	156.5	-2.8
Knific et al, 2022 [29]	15	8.75	11.01	9.5	163.5	161	-2.5

BA, bone age; CA, chronological age; TH, target height; AH, adult height; n/a, not available

Optimal Age at Which to Discontinue GnRHa Therapy for Central Precocious Puberty

Some studies have examined the timing at which treatment discontinuation is most likely to achieve the optimal AH [9–11,45]. Ohyama *et al.* reported changes in BA and the height standard deviation score (Ht-SDS) in 35 girls with idiopathic and organic CPP receiving GnRHa therapy [45]. Their results demonstrated that the Ht-SDS BA gradually increased from 10 years (-1.55 ± 1.07) to 11.5 years (-0.47 ± 0.84) and significantly decreased at 12 years (-1.06 ± 0.84). During treatment, advancement of bone maturation was noticeably suppressed during the period between BA of 11.0 and 11.9 years of age. The annual increments in height SDS relative to BA were higher when BA was younger than 12 years, but they subsequently declined to lower values when BA was 12 years or older. Taken together, these data suggested that extending the treatment beyond BA 12 years would not improve AH. The study concluded that therapy should be discontinued around BA 12 years on the Japanese version of the standardized RUS method (13 years on the TW-2 method). Prolonging treatment may increase the risk of psychosocial problems related to the suppression of sexual characteristics and induce future osteoporosis. Table 6 summarizes some previous reports, including the study by Ohyama *et al.*, examining the best timing at which to discontinue therapy to achieve the optimal AH. Most studies [2,7,9,10,41,45] found that discontinuing therapy at BA 12-12.5 years resulted in the greatest AH.

Table 6. Optimal age at which to discontinue GnRHa therapy for central precocious puberty

	Recommended BA at end of treatment (years)	Reason
Brauner et al, 1994 [41]	12.5	Patients had an AH well below the predicted AH at treatment discontinuation after achieving a final bone age of 11-12 years. Growth after the completion of treatment negatively correlated with CA.
Oostdijk et al, 1996 [7]	12.0 – 12.5	Residual growth potential was greater before the age of 12-12.5 years.
Ohyama et al, 1998 [45]	12.0	Height SDS per BA decreased after BA 12 years.
Bertelloni et al, 1998 [9]	11.5	AH was significantly greater when BA after termination was 11.5 years or less compared to 12 years or more.
Arrigo et al, 1999 [10]	12 – 12.5	Patients who ended treatment with a BA of 12 to 12.5 years had the highest AH.
Carel et al., 2008 [2]	11.0	AH correlated with post-treatment growth, which in turn correlated negatively with BA and CA at the start of treatment.

BA, bone age; CA, chronological age; AH, adult height

Conclusion

GnRHa therapy can halt the progression of idiopathic CPP in girls and contribute to improving their AH even if it cannot achieve the patient's full genetic potential for AH. The increase in height is more pronounced if therapy begins at age < 6 years. If slowly progressive CPP is diagnosed, the treatment must be carefully tailored to the pathophysiology of each patient. Because RCTs are difficult to conduct for ethical reasons, the efficacy of treatments needs to be examined in observational studies and case studies, which may help formulate new guidelines for treating girls with idiopathic CPP. Regarding the optimal timing of GnRHa discontinuation, a BA of 12 years is likely to produce the best AH outcome.

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