

Final height in central precocious puberty after long term treatment with a slow release GnRH agonist

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Abstract

Objective—To study the resumption of puberty and the final height achieved in children with central precocious puberty (CPP) treated with the GnRH agonist triptorelin.

Patients—31 girls and five boys with CPP who were treated with triptorelin 3.75 mg intramuscularly every four weeks. Girls were treated for a mean (SD) of 3.4 (1.0) years and were followed up for 4.0 (1.2) years after the treatment was stopped.

Results—The rate of bone maturation decreased during treatment and the predicted adult height increased from 158.2 (7.4) cm to 163.9 (7.5) cm at the end of treatment ($p < 0.001$). When treatment was stopped bone maturation accelerated, resulting in a final height of 161.6 (7.0) cm, which was higher than the predicted adult height at the start of treatment ($p < 0.001$). Height at the start of treatment was the most important factor positively influencing final height ($r = 0.75$, $p < 0.001$). Bone age at cessation of treatment negatively influenced final height ($r = -0.52$, $p = 0.03$). A negative correlation between bone age and height increment after discontinuation of treatment was observed ($r = -0.85$, $p = 0.001$). Residual growth capacity was optimal when bone age on cessation of treatment was 12 to 12.5 years. Body mass index increased during treatment and remained high on cessation. At final height, the ratio of sitting height to subischial leg length was normal. Menarche occurred at 12.3 (1.1) years, and at a median (range) of 1.1 (0.4 to 2.6) years after treatment was stopped. The ovaries were normal on pelvic ultrasonography.

Conclusions—Treatment of CPP with triptorelin increases final height, with normal body proportions, and seems to increase body mass index. The best results were achieved in girls who were taller at the start of treatment. Puberty was resumed after treatment, without the occurrence of polycystic ovaries.

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For more than a decade children with central precocious puberty (CPP) have been treated

with gonadotrophin releasing hormone (GnRH) agonists with variable potencies and different routes of administration. GnRH agonist treatment causes hormonal suppression and thereby influences secondary sexual characteristics, growth, and bone maturation.¹⁻⁸

Some investigators suggest that delaying puberty does not improve final height prognosis, as the decreased rate of epiphyseal maturation is offset by a decrease in growth hormone secretion and growth rate.⁹

Recently, various studies reporting final height and the reversibility of the gonadal axis on discontinuation of treatment have been published.¹⁰⁻¹⁷ Most of these results are based upon agonist treatment given by daily subcutaneous injections or intranasal application. It was suggested that auxological improvement depends on a continuous and full suppression of gonadal steroid production.¹⁸ Furthermore, improved results have been documented in children with young (bone) ages.¹⁹

We have shown that treatment of children with CPP with the slow release GnRH agonist triptorelin is effective in continuous suppression of gonadal activity.^{7, 20}

In this paper we present the data on the resumption of puberty and the adult height attained in children with CPP who were treated with the slow release GnRH agonist triptorelin.

Methods

PATIENTS

Thirty six patients (31 girls and five boys) with CPP achieved a final height following treatment with triptorelin (D-Trp6-LHRH) at a mean dose of 96 (SD 25) $\mu\text{g}/\text{kg}$ intramuscularly repeated every four weeks. The diagnostic criteria for CPP have been described in the past and are summarised as follows: the appearance of secondary sexual characteristics before the age of 8 and 9 years in girls and boys respectively, a bone age/height age ratio ≥ 1 , including a pubertal luteinising hormone (LH) response in a GnRH test.⁷ Twenty eight patients (25 girls and three boys) received only triptorelin, whereas eight patients (six girls and two boys) were treated with buserelin subcutaneously (27-30 months) or cyproterone acetate orally (6-40 months) before starting triptorelin.

A computerised tomographic (CT) scan or magnetic resonance imaging (MRI) of the brain, or both, was performed in all patients: in

24 girls CPP was considered idiopathic, in four girls there was infantile encephalopathy, two girls had been operated on for an astrocytoma, and in one girl a hamartoma was found. In none of the girls with organic CPP was growth hormone secretion evaluated. Three of the five boys were suffering from neurofibromatosis, one boy was operated on for an arachnoid cyst, and in one boy the CPP was idiopathic. None of the boys with neurofibromatosis underwent radiotherapy or surgery. Because no growth impairment was observed in these three boys, growth hormone secretion was not evaluated. The boy operated on for an arachnoid cyst was evaluated before GnRH agonist treatment was started, and a normal growth hormone response to arginine stimulation ($\text{GH} > 20 \text{ mU/l}$) was shown.

The patients were treated for at least two years. After discontinuation of triptorelin they were evaluated each subsequent year until the final height was achieved. Final height was considered to be attained when the bone age was ≥ 15.0 years in girls and ≥ 16.0 years in boys or when height velocity was $< 1.0 \text{ cm/year}$ for a minimum period of one year, or both. Once the final height was attained, pelvic ultrasonography was performed using Acuson equipment (Mountain View, California, USA) with 3.5 or 5 MHz transducers.

GROWTH EVALUATION

On initiating the study and subsequently every three months during the treatment and every six to 12 months after the treatment was discontinued, the patients underwent a physical examination including measurement of height, sitting height, and weight, and recording of secondary sexual characteristics. Weight was expressed as a quotient using the body mass index (BMI) (weight/height^2) and BMI SD score for chronological age (BMI SDS_{CA}) and bone age (BMI SDS_{BA}), using French reference values.²¹

Height was expressed as SD score for chronological age and bone age, using national growth references.²² When measured parental heights were available, target height was calculated using the following formula: (sum of the height of the parents ± 12) / 2 + 3 cm. Target height range was defined as target height ± 1 SD. For adult females 1 SD amounts to 6.2 cm.²²

The ratio of sitting height to subischial leg length was expressed as SD score for chronological age (SH/LL SDS_{CA}) using reference values obtained from the Zürich longitudinal growth study.²³

Bone age was determined by one observer (WO) according to the method of Greulich and Pyle, and predicted adult height was determined using the tables of Bayley and Pinneau.²⁴

Strictly speaking, adult height prediction is only applicable under physiological circumstances, and has an inherent tendency to overestimation in CPP. However, changes in predicted adult height can reasonably be used as a measure of efficacy using treatment such as a GnRH agonist. In this study we have defined

change in predicted adult height as the difference between final height and the predicted adult height at the start of treatment.

STATISTICAL ANALYSES

All results are expressed as mean (SD), unless indicated otherwise. In the auxological evaluation the Wilcoxon signed rank test was used to determine differences within each group and the Mann-Whitney U test was used for determining differences between groups. Pearson correlation analysis was carried out to assess linear associations. To determine the effects of a number of auxological variables upon final height, a stepwise multiple regression analysis was performed using final height as the dependent variable. The variables were chronological age, bone age, height, and BMI (all at the start of treatment); bone age at the time of discontinuation of treatment; target height, duration of treatment, and chronological age at attainment of final height.

Written informed parental consent was obtained before the start of treatment. The study was approved by the ethics committees of the participating university hospitals.

Results

During treatment, regression in secondary sexual characteristics occurred because prepubertal oestradiol and testosterone levels were attained in girls and boys, respectively, as has been reported in the past.⁷⁻²⁰ No local or systemic side effects were observed. One girl developed type 1 diabetes mellitus several months after discontinuation of triptorelin.

AUXOLOGICAL EVALUATION

No significant differences in chronological age, bone age, height, predicted adult height at the start of treatment, or in final height and target height were found between the group of previously untreated patients compared to the previously treated group (Mann-Whitney U test). Therefore, all data were compiled together.

Baseline data

In girls, chronological age at the start of triptorelin treatment was 7.7 (0.8) years (table 1). The onset of puberty as reported by the parents was 6.0 (2.0) years. In boys, chronological age at the start of treatment was 7.9 (1.9) years.

The actual height at the start of treatment in girls is reported in table 1. It was 140.1 (8.4) cm (+2.10 (2.21) SD score) in boys.

Patients were treated for a period of 3.4 (1.1) (F) and 4.2 (0.8) (M) years, respectively, and were followed up for 4.0 (1.2) (F) and 3.9 (0.9) (M) years after the discontinuation of treatment.

Height velocity

Before initiating treatment the height velocity was 8.0 (2.3) cm/year in girls and 10.4 (4.8) cm/year in boys.

In girls, during treatment height velocity decreased to low values in the last year of treatment (table 2). An increase in height velocity

Table 1 Effect of triptorelin treatment in girls on mean (range or SD) chronological age, bone age, actual height, predicted adult height, height SD score for chronological age and bone age, sitting height/leg length SD score for chronological age, and body mass index SD score for chronological and bone age, evaluated at the start and at the end of treatment and at final height

	No	Start of treatment	End of treatment	Last visit
Chronological age (years)	31	7.7 (5.1 to 9.2)	11.1 (9.4 to 13.1)	15.1 (12.7 to 17.5)
Bone age (G&P) (years)	31	10.8 (9.4 to 12.5)	12.5 (11.5 to 13.5)	16.0 (15.0 to 17.0)
Actual height (cm)	31	137.3 (117.9 to 152)	152.4 (140.6 to 161.8)	161.6 (146 to 174.9) ^{a,b}
Predicted adult height (cm)	31	158.2 (145.5 to 176)	163.9 (148.7 to 181.6) ^a	—
Height SDS _{CA}	31	1.60 (1.21)	0.58 (1.10) ^c	-1.08 (1.12) ^{e,d}
Height SDS _{BA}	31	-1.31 (0.95)	-0.71 (0.98) ^c	-1.08 (1.12) ^{d,e}
Sitting height/leg length SDS _{CA}	15	-0.36 (1.53)	0.06 (1.21)	-0.08 (0.97)
Body mass index as:				
SDS _{CA}	30	1.70 (1.31)	1.80 (1.41)	1.44 (1.46)
SDS _{BA}	30	0.66 (1.05)	1.29 (1.29) ^c	1.44 (1.45) ^c

G&P = Greulich and Pyle.

a = $p < 0.001$ compared with predicted adult height at the start of treatment; b = $p < 0.001$ compared with predicted adult height at the end of treatment; c = $p < 0.001$ compared with start of treatment; d = $p < 0.001$ compared with the end of treatment; e = $p < 0.05$ compared with the start of treatment.

was only observed in the first year after discontinuation of treatment. In boys the same pattern was observed (data not shown).

Change in bone maturation and predicted adult height

Bone age at the start of treatment was 10.8 (0.7) years in girls (table 1) and 11.0 (2.6) years in boys. In girls, bone maturation, expressed as Δ bone age / Δ chronological age ratio, decreased during treatment (table 2),

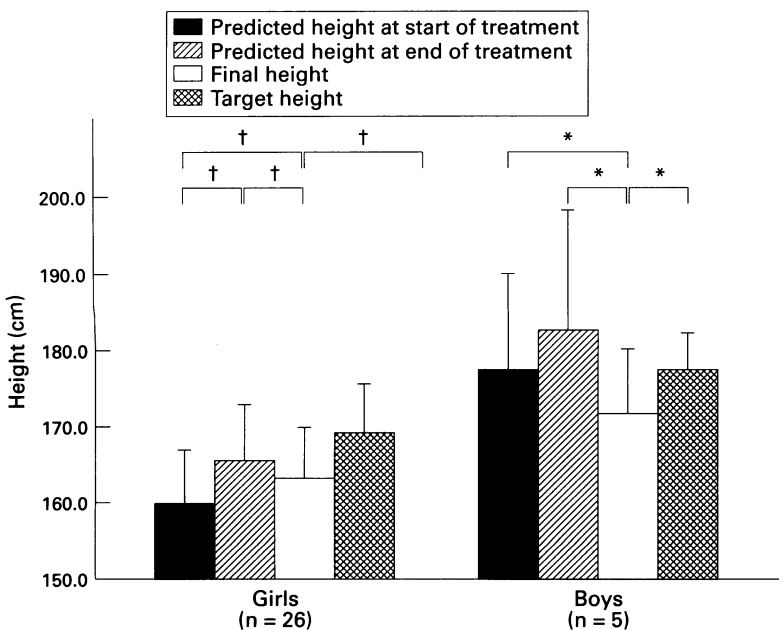


Figure 1 Predicted, final, and target height in girls ($n=26$) and boys ($n=5$) during and after treatment with triptorelin. * $p < 0.05$, † $p < 0.01$.

Table 2 Height velocity and bone maturation (Δ bone age/ Δ chronological age) during and after discontinuation of triptorelin treatment in girls

	No	Height velocity (cm/year)	No	Δ Bone age/ Δ chronological age
Whole treatment period	31	4.5 (0.9)	31	0.52 (0.21)
Last year of treatment	25	3.7 (1.0)	19	0.47 (0.34)
1st year after stopping treatment	25	4.8 (1.8)*	19	0.81 (0.36)*
2nd year after stopping treatment	25	2.9 (1.5)†‡	19	1.34 (0.36)†‡

* $p < 0.001$ compared with the last year of treatment; † $p < 0.01$ compared with the 1st year after stopping treatment; ‡ $p < 0.01$ compared with the last year of treatment.

resulting in an improvement of predicted adult height at the start of treatment compared to predicted adult height at the point of discontinuation of treatment (table 1) (fig 1).

After discontinuation of treatment bone maturation accelerated immediately in the first year, with higher Δ bone age / Δ chronological age ratios in the second year (table 2).

In boys, the Δ bone age / Δ chronological age ratio during treatment was 0.56 (0.34), resulting in an improvement of predicted adult height from 177.4 (12.6) cm at the start of treatment to 182.5 (15.7) cm at the point of cessation of treatment (fig 1). After discontinuation of treatment the same pattern was observed as in girls (data not shown).

Final height

In girls, the changes in height velocity and bone maturation resulted in a final height of 161.6 (7.0) cm, which was less than that predicted at cessation of treatment [163.9 (7.5)] and less than target height [168.7 (6.4) cm] [+0.06 (1.03) SDS] ($n=26$), but higher than predicted adult height at the start of treatment [158.2 (7.4) cm] (fig 1) (table 1). A positive change in predicted adult height of 3.5 (4.2) cm (range -4.8 to +10.5 cm) was achieved.

In the five boys, final height was 171.5 (8.5) cm [-1.57 (1.27) SDS] which, similarly, was less than predicted at cessation of treatment, but also less than the predicted adult height at start of treatment.

Correlation between final height and other variables

In girls a positive correlation was shown between final height and height at the beginning and at the end of treatment ($r = +0.75$, $p < 0.001$, and $r = +0.84$, $p < 0.001$ respectively). A negative correlation was observed between final height and bone age at the end of treatment ($r = -0.52$, $p = 0.03$). Furthermore, a negative correlation between chronological age and bone age at the end of treatment and the height increment after treatment was found ($r = -0.45$, $p = 0.005$, and $r = -0.85$, $p < 0.001$ (fig 2), respectively). No linear correlation was observed between final height and chronological age or bone age at start of treatment or the duration of treatment. A weak correlation was demonstrated between final height and target height ($r = +0.32$, $p = 0.05$).

Stepwise multiple regression analysis revealed that final height (y) was influenced most

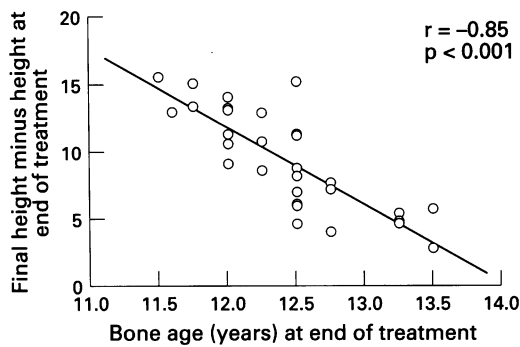


Figure 2 Final height minus height at the end of triptorelin treatment as a function of bone age (years) at the end of triptorelin treatment in girls ($n = 31$).

significantly by height at the start of treatment (x_1). Other significant factors were the bone age at the point of starting of treatment (x_2) and at discontinuation of treatment (x_3) and the duration of treatment (x_4) ($y = +0.91 \times x_1 - 3.6 \times x_2 - 5.0 \times x_3 + 1.5 \times x_4 + 132.5$; $R^2 = 0.89$; residual SD = 2.46; $p < 0.001$).

Twenty four of the 31 girls showed a positive change in predicted adult height (median 5.2 cm, range 0.5 to 10.5 cm) (group A); however, seven of the 31 girls (group B) reached a final height below predicted adult height at start of treatment (median -2.9 cm, range -0.9 to -4.8 cm). The most important differences between these groups were a younger age at start of treatment in group A [7.5 (0.8) v 8.4 (0.6) years, $p = 0.01$], a higher bone age/chronological age ratio at start of treatment in group A [1.45 (0.15) v 1.29 (0.08), $p = 0.01$], and a longer period of treatment in group A [3.7 (1.1) years v 2.5 (0.7) years, $p = 0.02$].

In 26 girls target height was available. Sixteen of these girls (62%) achieved final height within the target height range, whereas 10 did not.

Change in body proportions and composition

The SD score of the ratio of sitting height to subischial leg length at final height was normal in girls, at 0.07 (0.98) ($n=26$). In 15 girls the ratio SHLL SDS_{CA} was known during treatment and at final height (table 1). No significant changes were observed.

BMI SDS_{CA} in girls at start of treatment was higher than the reference population and it did not change significantly during and after treatment (table 1). BMI SDS_{BA} at start of treatment was normal and increased during treatment (table 1). It did not change after discontinuation of treatment. The same pattern was observed in boys.

We compared the BMI SD score data of our patients with those from a group of 23 girls treated daily with subcutaneously buserelin, another GnRH agonist, for two years.³ In this buserelin group [chronological age 6.0 (1.7) years; bone age 9.9(2.2) years at the start of treatment] BMI SDS_{CA} and BMI SDS_{BA} were calculated at the start and at the end of buserelin therapy (BMI at final height was not known in this group of girls). BMI SDS_{CA} at the start and at the end of the treatment was 1.07 (1.00) and 1.30 (1.05) respectively, not significantly different from the equivalent data

in our triptorelin group. BMI SDS_{BA} at the start and at the end of buserelin was 0.28 (0.64) and 0.06 (0.75) respectively. BMI SDS_{BA} at the start of buserelin treatment was not significantly different from BMI SDS_{BA} at the start of triptorelin. On the other hand BMI SDS_{BA} at the end of treatment was significantly higher in the triptorelin group than in the buserelin group ($p < 0.001$). (There was no difference in bone age at the start of therapy between the two groups.)

MENSES AND PELVIC ULTRASOUND EVALUATION

Menarche occurred at 1.1 years (median) (range: 0.4 to 2.6 years) after discontinuation of treatment and at a chronological age of 12.3 (1.1) years. At the final consultation, five of the 31 girls were using oral contraceptives. The menstrual cycles were regular in 26 out of the 31 girls.

Pelvic ultrasonography was performed in 22 girls. Four of them were using contraceptives and in all four girls normal ovaries were observed. In the remaining 18 girls, the volume of the uterus 33.9 (15.6) cm^3 , which represents the upper limit of the normal adult volume. The volumes of the ovaries were within the normal range, at 7.9 (3.9) cm^3 compared to the reference value of 7.4 (4.8) cm^3 .²⁵

In four girls, one of the ovaries was larger than normal. In two of these, 2-3 cysts with a diameter ≤ 0.6 cm were visualised, coinciding with the norm for this stage of puberty.¹⁷ In the remaining two girls, 8-10 cysts of ≤ 0.6 cm diameter were observed. The menstrual cycles were regular in these four girls. In the ovaries of the remaining 14 girls, a maximum of two to six cysts with a diameter ≤ 0.9 cm were observed. In two of the 14 girls, cysts were documented with a diameter of 2.0 cm. However, this was observed 12 to 14 days after the first day of the menstruation, that is, at the point of ovulation.

Discussion

This study shows that adult height in girls can be increased by treatment with the slow release GnRH agonist triptorelin, although less than would be expected at the point of discontinuation of treatment.

Final height in our girls was 161 (7.0) cm, greater than the final height of untreated girls in the studies of Thamdrup²⁶ [151.3 (8.8) cm, $n = 26$], Sigurjonsdottir and Hayles²⁷ [152.7 (8.0) cm, $n = 34$], and Paul *et al*¹⁹ [152.7 (8.6), $n = 93$]. The positive change in predicted adult height of 3.5 cm lies between the values of 2.4 to 6.2 cm reported in two other studies where daily subcutaneous preparations were used.^{11 12} Using triptorelin a greater improvement in predicted adult height of 6.5 (1.4) cm was reported by Brauner *et al*, despite the fact that the inclusion criteria used were similar to ours.¹³ The most remarkable positive change in predicted adult height—10 cm—was described by Paul *et al* in a group of girls treated before 5 years of age.¹⁹ This tendency for young patients to obtain a greater positive change in predicted adult height was also observed in our population: in the girls who had a positive change in

predicted adult height of 5.2 cm (range 0.5 to 10.5 cm) (group A), chronological age was significantly lower than in those girls who had a negative change in predicted adult height. Therefore age at the onset of treatment seems to play an important role. Only four girls in our group were younger than 7 years of age at the start of treatment; hence we could not show a significant relation between age at start of treatment and the final height obtained.

Height at start of treatment proved to be the most important positive factor influencing final height, as demonstrated by multiple regression analysis and by a positive correlation coefficient ($r = +0.75$), a characteristic that is also described in normal puberty.²⁸ Final height showed a weak association with target height, as also shown by Paul *et al.*¹⁹ Only 62% of the girls with a known target height reached a final height within the target height range. However, this weak association between target height and final height is similarly identified in the normal population (0.45).²⁹

In contrast to other studies, no improvement of adult height was demonstrated in boys.¹¹⁻¹⁹ The most plausible explanation for this difference is that three out of the five boys were suffering from neurofibromatosis, a condition which itself is associated with growth impairment, and in which the development of complications such as optic nerve glioma may lead to growth hormone insufficiency. On the other hand, in some cases growth impairment has been described independently of growth hormone levels.³⁰ In our patients growth hormone secretion was not evaluated.

The difference in final height as predicted at the point of discontinuation of treatment and the actual final height attained is caused by a moderate growth acceleration after cessation of treatment and a definite accelerated bone maturation within the same period. The same tendency has been described by Oerter *et al.*¹² As suggested before, the post-therapy level of gonadotrophins and sex steroids rises more rapidly than in normal puberty, and higher levels are reached in a shorter period of time.²⁰ This results in a shorter period of growth and eventually a final height that is less than the predicted adult height at the point of discontinuation of treatment.

In addition to height at start of treatment, bone age at the point of discontinuation of treatment is another important negative factor contributing to final height. As shown in fig 2, residual growth capacity is greater before a bone age of 12.0 to 12.5 years. For this reason discontinuation of GnRH treatment might be considered at a bone age of 12 to 12.5 years.

Triptorelin treatment did not influence body proportions, as normal ratios of sitting height to subischial leg length were observed at the point when final height was reached.

In girls, BMI SDS_{CA} was increased at start of treatment and did not change during or after discontinuation of treatment. On comparison of our data with those of Marti-Henneberg, who described the normal course of BMI during early, normal, and late puberty, the increased BMI SDS_{CA} at start of treatment

appears to be a natural event.³¹ Since children with CPP who had been exposed to sex steroids underwent a pubertal growth spurt and subsequently developed accelerated bone age, it would be better to use the index BMI SDS_{BA}. Using this index, a comparison can be made between the girls with CPP and those with normal age of onset of puberty at similar bone ages. The index was normal at start of treatment and increased during treatment, suggesting that triptorelin increases BMI, as no change in BMI SDS_{BA} was observed during buserelin treatment.

In our patients a rapid resumption of puberty was observed, menarche occurring 1.1 years (range 0.4 to 2.6 years) after withdrawal of treatment, at a mean age of 12.3 (1.1) years.²⁰ This is comparable with the results of other investigators.⁸⁻³² Ultrasound evaluation showed normal ovaries 4.0 (1.2) years after discontinuation of treatment. In contrast to the report by Adams *et al.*, no evidence of polycystic ovaries was found.¹⁷

We conclude, therefore, that treatment with the depot GnRH agonist triptorelin increases final height in girls without giving rise to abnormal body proportions. The best results are obtained in girls with a greater height at the point of starting treatment. After withdrawal of therapy, resumption of puberty occurs rather rapidly, without evidence for development of polycystic ovaries. Triptorelin seems to increase BMI. From an auxological point of view, discontinuation of triptorelin in girls might be considered at a bone age of 12.0 to 12.5 years.

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