CLINICAL STUDY

Idiopathic precocious puberty versus puberty in adopted children; auxological response to gonadotrophin-releasing hormone agonist treatment and final height

M J E Kempers and B J Otten¹*Department of Pediatric Endocrinology, Emma Children's Hospital, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands and**¹Department of Pediatric Endocrinology, University Medical Center St Radboud, Nijmegen, The Netherlands**(Correspondence should be addressed to B J Otten, Department of Pediatric Endocrinology, University Medical Center St Radboud, PO Box 9101, 6500 HB Nijmegen, The Netherlands; Email: B.Otten@ckskg.azn.nl)*

Abstract

Objective: The objective of this study was to evaluate the characteristics of puberty and response to gonadotrophin-releasing hormone (GnRH) agonist treatment in adopted children compared with children with idiopathic precocious puberty (IPP).

Methods: We studied 17 girls with central IPP (group A) and 11 girls adopted from Asia and Central and South America (group B) with respect to auxological data at presentation of puberty and response to GnRH agonist treatment.

Results: In adopted girls, age at onset of puberty was later and duration of treatment was shorter. At the start of treatment, height-standard deviation score (H-SDS) was +1.67 s.d. in group A. In group B, H-SDS was comparably increased (+0.04 s.d.) assuming that the mean H-SDS in their native country is lower than the mean on the Dutch curve. During treatment, H-SDS decreased in both groups. Group A reached a final height (FH) of 166.2 cm (−0.3 s.d.) and group B of 156.1 cm (−1.9 s.d.). Predicted adult height (PAH) at the start of treatment underestimated FH in group A and overestimated FH in group B. At the end of treatment, PAH overestimated FH in both groups. The SDS for weight was above the mean in both groups at the start of treatment and increased even more during treatment. The age of occurrence of menses after treatment was stopped was the same in both groups (12.7 and 12.8 years respectively).

Conclusion: Despite the difference in timing of puberty between girls with IPP and adopted girls with early puberty, their response to treatment was similar in many aspects.

European Journal of Endocrinology 147 609–616

Introduction

In puberty, the activation of the hypothalamic–pituitary–gonadal axis results in the development of secondary sexual characteristics, increased growth velocity and accelerated bone maturation. In precocious puberty, premature activation of this axis occurs; this is defined as the development of pubertal signs in girls before 8 years and in boys before 9 years. Due to a shortened prepubertal growth period and a diminished pubertal growth spurt, adult height is impaired.

Precocious puberty in general is more frequent in girls. The majority of girls have idiopathic precocious puberty whereas, in boys, central nervous system (CNS) pathology, such as intracerebral tumours, is more common (1).

A striking observation is that early or precocious puberty is frequently observed in adopted children (2–6). The cause is not known but improved nutritional

and social conditions together with the catch-up growth following adoption might trigger the onset of puberty (2, 5). In the general population, the 'secular trend' towards earlier puberty and increased final height is considered to be a result of improved socio-economic development. Proos *et al.* (7) suggested some parallelism between the occurrence of early puberty in adopted girls and this secular trend. A recent article by Krstevska-Konstantinova *et al.* (6) suggested that in immigrant children the exposure to endocrine disruptors such as organochlorine pesticides might also influence the timing of puberty.

Treatment of precocious puberty consists of gonadotrophin-releasing hormone (GnRH) agonists. One of the main goals of treatment is to improve final height by slowing down bone maturation. In adopted children, the genetic growth potential in the native country is on average below the mean of that in the foster country. Therefore, adopted children with precocious or early

puberty might suffer even more in absolute terms of final height deficit. In the University Medical Center St Radboud in Nijmegen, adopted children make up a considerable percentage (i.e. 20%) of the total group of children treated with GnRH agonists; this percentage is similar to that reported in a Belgian study (6).

In this article, we report the auxological data of adopted children and children with idiopathic precocious puberty before, during and after GnRH agonist treatment. The characteristics of (early) puberty and response to GnRH agonists of both groups were analysed and compared.

Patients and methods

Patients

During the last decade 59 patients (51 girls, 8 boys) were treated with GnRH agonists in the University Medical Center St Radboud in Nijmegen because of signs of early pubertal development.

After exclusion of children with CNS pathology, children additionally treated with growth hormone and native Dutch children treated for impaired height prognosis (without fulfilling the strict age criteria of precocious puberty), 29 children (28 girls, 1 boy) were left. For analytical reasons the boy was excluded. Of the remaining 28 girls, 17 had idiopathic central precocious puberty, defined as pubertal signs before the age of 8 years (group A) and 11 girls were adopted (group B). In the group of adopted girls, the country of origin and age at arrival were recorded. Nine children came from Asia (India, Indonesia, Korea and Sri Lanka) and two came from Central and South America (Colombia and Honduras). There was a great difference in age on arrival in Holland, from 1-month old to 87-months old, mean age 31 months. In only seven children was the height at adoption known; mean height was -2.4 S.D. (range -0.3 S.D. to -3.9 S.D.) on the Dutch standard curve. Weight at adoption was known in five children; only two children had weight-standardized scores (SDS) < -2 S.D. (see Methods).

All patients included had a pubertal response to the GnRH test (follicle-stimulating hormone and luteinizing hormone >10 IU/l). They received intramuscular injections with Triptoreline (Decapeptyl, Ferring BV, The Netherlands) at a dose of 3.75 mg every 4 weeks.

Treatment was stopped when chronological age was above 11 years, when height velocity had decreased to less than 4 cm/year, when prognosis of final height was satisfactory and/or when the psychological condition of the patient was considered to be mature enough to cope with puberty.

In Table 1 the mean chronological age at the start of puberty, at the start of treatment and the duration of treatment are given. The age at which pubertal signs first appeared was assessed from the case history. In group B, three girls were older than 8 years (respectively

Table 1 Mean chronological age at the start of puberty, at the start of treatment and the duration of treatment for both groups.

	Group A	Group B
Age at onset of puberty (years)	6.4	7.9
(range)	(3.0–7.8)	(6.0–11.0)
Age at onset of treatment (years)	7.9	9.4
(range)	(4.0–9.7)	(6.4–11.4)
Duration of treatment (months)	41	29
(range)	(20–84)	(17–50)

8.5, 10.0 and 11.0 years). Because we were interested in the response to GnRH treatment in all adopted girls, the age at onset of puberty was not used as an exclusion criterion and these three children were included in group B.

Methods

Of all patients, growth data were assessed retrospectively at regular times before, during and after treatment (i.e. from 6 months before until 2 years after the start and end of treatment respectively) as well as final outcome. The time-courses around the start and the end of treatment were chosen because changes are most marked in these periods. Growth data consisted of height measured with a stadiometer, weight and bone age (BA). Height velocity was calculated in cm/year. The SDS for height (height-SDS) was calculated using the data according to Roede & Van Wieringen (8). BA was scored by one observer (B J O) according to Greulich & Pyle (9). The SDS for weight (weight-SDS) was determined using the data of Roede & van Wieringen (8). Heights and weights were evaluated for normal children per chronological year. Analysis showed a normal distribution when an inversed body mass index $((\text{weight}/\text{height}^2)^{-1})$ was used. With the help of polynomial regression, formulas were made and individual SD scores could be calculated.

The predicted adult height (PAH) was calculated using the method of Bailey & Pinneau (10) and Greulich & Pyle (9). Individual target heights were not known for the adopted girls. Final height was considered to have been achieved when height velocity was <1 cm/year and BA was >15 years.

Statistics

Values are reported as means, unless otherwise stated. Statistical analysis was done by performing a Student's *t*-test; $P < 0.05$ was considered significant. Confidence intervals were calculated using SPSS 10.0 software (SPSS Inc., IL, Chicago, USA).

Table 2 Height-SD, height velocity, weight-SD, BA minus CA* and PAH at the moment when treatment was started and stopped and final height and target height for both groups. The lower/higher 95% confidence intervals are shown in square brackets.

		Group A		Group B
Height-SD	Start	1.7 [0.9/2.4]	Start	0.0 [−0.9/+0.9]
	Stop	0.8 [0.1/1.5]	Stop	−0.6 [−1.6/+0.4]
Height velocity (cm/year)	Start	9.6 [8.4/10.9]	Start	10.0 [5.3/14.7]
	Stop	3.4 [2.7/4.1]	Stop	2.6 [1.6/3.6]
Weight-SD	Start	0.7 [0.1/1.3]	Start	0.2 [−0.5/+1.0]
	Stop	1.2 [0.4/1.9]	Stop	0.9 [0.2/1.7]
BA − CA* (year/year)	Start	2.2 [1.9/2.6]	Start	1.9 [1.2/2.6]
	Stop	0.6 [0.3/0.9]	Stop	0.8 [0.0/1.5]
PAH (cm)	Start	164.2 [158.9/169.5]	Start	158.1 [155.7/160.4]
	Stop	168.8 [163.6/174.0]	Stop	159.6 [151.9/167.4]
Final height (cm)		166.2 [161.7/170.7]		156.1 [151.7/160.5]
Target height (cm).		168.8 [164.6/172.9]		

Results

Table 2 summarizes the different parameters, i.e. height-SDS, height velocity, weight-SDS, 'BA minus chronological age (CA)' and PAH at the point at which treatment was started and stopped. Figures 1 to 5 present graphic representations of these parameters during the two time-courses.

Height velocity/height-SDS (Figs 1 and 2)

The pattern of height velocity was the same in both groups. Before the start of treatment, height velocity was pubertal (9.6 and 10.0 cm/year respectively) which decreased significantly during the first 6 months

of treatment ($P < 0.01$ and < 0.05 respectively). During treatment, height stabilized at about 4 to 5 cm/year in both groups. After treatment was stopped, height velocity increased initially (only significantly in group A, $P < 0.05$) but in the second year after the end of treatment height velocity decreased in both groups ($P < 0.01$).

In both groups, height-SDS was elevated before treatment was started (assuming that the adopted girls should grow below the Dutch mean). During treatment, group A showed the most marked decrease just before treatment was stopped ($P < 0.01$). In group B, the decrease in height-SDS during treatment was already significant in the second 6 months of treatment ($P < 0.01$). The decrease remained significant during the whole course of treatment. After treatment was

Figure 1 Height velocity (HV) (cm/year) around the start and the end of treatment in groups A (■) and B (□).

Figure 2 Height-SDS around the start and the end of treatment in groups A (■) and B (□). The broken lines represent final height-SDS for group A (dashed line) and group B (dashed and dotted line).

stopped, height-SDS decreased progressively in both groups ($P < 0.01$).

Weight-SDS (Fig. 3)

SD scores for weight were increased in both groups during the whole time-course of treatment although group A had consistently higher SD scores than

group B. During treatment, a significant increase was seen ($P < 0.05$ and < 0.01 respectively); this was most marked in the first 6 months of treatment for group B ($P < 0.01$). After treatment was stopped, weight stabilized in group B but further increased in group A, although not significantly.

At final height, weight was compared with adult reference ranges for body mass index and weight-for-

Figure 3 Weight-SDS around the start and the end of treatment in groups A (■) and B (□).

Figure 4 BA minus CA around the start and the end of treatment in groups A (■) and B (□).

height (WFH) index (8). Body mass indexes were 23.1 and 20.8 kg/m² respectively (normal range 19–25). The WFH index was, on average, too high in both groups: 80% of girls in group A and 91% of the girls in group B were above the mean.

BA versus CA (Fig. 4)

BA was advanced for CA at the start of treatment in both groups (by 2.2 and 1.9 years respectively). During treatment, BA increased, although less than

Figure 5 PAH (cm) around the start and the end of treatment in groups A (■) and B (□). The broken lines represent final height (cm) for group A (dashed line) and group B (dashed and dotted line).

1 year/year CA; consequently BA for CA was less advanced at the end of the treatment period (with 0.6 and 0.8 years respectively).

PAH (Fig. 5)

In group A, mean PAH at the start of treatment (164.2 cm) was 4.6 cm below target height. During treatment, PAH increased to 168.8 cm at the time when treatment was stopped ($P < 0.01$), which overpredicted final height by 2.6 cm. In group B, mean PAH at start of treatment (158.1 cm) was 2.0 cm above final height. During treatment, PAH fluctuated. At the end of treatment, PAH (159.6 cm) overpredicted the final height by 3.5 cm.

Final height

In group A, the mean final height was 166.2 cm (-0.3 s.d.), which was 2.6 cm below target height. The variation in final height was large, ranging from 142.3 cm (-4.2 s.d.) to 175.3 ($+1.1$ s.d.). In seven girls, the final height was above target height (mean difference 3.2 cm); ten girls had a final height below their target height (mean difference 6.6 cm). In group B, final height was 156.1 cm (-1.9 s.d.), ranging from 145.3 (-3.7 s.d.) to 171.3 ($+0.5$ s.d.) cm.

Menses

In both groups, three girls had menses before the start of treatment. Withdrawal bleeding during the first weeks of treatment occurred in four girls of group A and five girls of group B; two girls in both groups already had menses before the start of treatment. After treatment was stopped menses (re)occurred in all girls. The mean age did not differ much between both groups, 12.7 and 12.8 years respectively. It took about a year before menses (re)occurred (1.3 years and 1.1 years respectively). When menses had occurred before treatment was started, the reoccurrence was earlier with a mean of 1.1 (A) and 0.7 years (B) respectively.

Discussion

In a relatively large number of children with precocious puberty, especially girls, no satisfactory explanation can be found for the premature activation of the gonadal axis, designated as 'idiopathic precocious puberty'. In adopted children, in whom earlier occurrence of puberty is a well-known phenomenon, etiology is not fully understood either. It is speculated that in the latter group improved nutritional and socio-economic conditions contribute to the early activation of the gonadal axis. In addition, a component of intra uterine

growth retardation is also possible or presumable in some of the formerly deprived children.

GnRH agonists, inducing desensitization of the pituitary response to GnRH, are well established in the treatment of central precocious puberty. Several reports have been published about their effect on secondary sexual characteristics, growth and bone maturation. Only a few discuss treatment in adopted children (2, 3, 11–13).

As far as we know, a comparative analysis of baseline and GnRH agonist treatment characteristics for idiopathic precocious puberty and early puberty in adopted girls has never been fully reported. We have described the characteristics of puberty and response to GnRH agonists in a comparative manner in these two groups.

For the idiopathic group, we selected girls who were confined to the age criterion of idiopathic precocious puberty, i.e. occurrence of puberty before 8 years. In the adopted girls, mean age at start of puberty (7.9 years) was just below the age criterion for idiopathic precocious puberty. In this group, three children exceeded the age of 8 years. To avoid a selection within the group of adopted children they were included in the analysis.

As would be expected, height-SDS in the idiopathic group was increased above average ($+1.67$ s.d.) when treatment was started. For adopted girls, height-SDS seemed to be comparably increased ($+0.04$ s.d.), assuming that the mean height-SDS in their native country is about 2 s.d. lower than the mean on the Dutch curve (3). This increased height-SDS at the time puberty started is similar to that described for adopted girls in Italy (2). After treatment was stopped, height velocity failed to increase to the same magnitude as before treatment, the BA minus CA increased and height-SDS decreased. This might indicate that the growth potential after treatment with GnRH analogues is diminished.

In the idiopathic group, the PAH at the start of treatment underestimated the final height. Although the increment in PAH would suggest a positive effect of treatment, PAH gradually overestimated final height. In contrast, PAH in group B overestimated final height during the whole time-course of treatment. The net increment in PAH during treatment is frequently reported, as is the overprediction of PAH at the end of treatment (14–17). It seems that the prediction of adult height is inaccurate in these children. In part this could be due to the fact that prediction methods are primarily based on the data of normal children from developed countries, without precocious puberty. Our observations underline a recent review by Hintz (18) suggesting that predictions of adult height in individuals, especially those who have abnormalities of growth, should be interpreted carefully.

The difference between target height and PAH at the start of treatment can be considered as an indication for

the loss of growth potential as a consequence of the disease. The calculated loss in height potential due to the disease is 4.6 cm for group A. When the difference between final height and PAH at the start of treatment is considered as an indication for the gain of treatment, group A gained 2.0 cm from treatment. They reached a final height near their target height. For the adopted girls, PAH at the start of treatment was higher than their final height. From the 'increased' PAH at the start of treatment it might be concluded that treatment was not necessary. However, it is debatable whether reaching a final height comparable to -2.0 S.D. on the Dutch standard is optimal, since these children grow up in better socio-economic conditions where the mean height of children is more than 12 cm higher. Since in most adopted children, as catch-up growth is seen in the first years after arrival, a better height prognosis might be expected. Japanese immigrants born and grown up in the USA become taller than their native Japanese peer group (19). Oostdijk *et al.* (3) investigating adopted children from various countries found that the mean final height was below the final height for Dutch girls, but almost similar to the final height of girls in their native country. Linear growth and final height seemed to be influenced by the timing of puberty.

We can only speculate whether final height would have deteriorated or perhaps would have improved if treatment had not been started at all. Virdis *et al.* (2), comparing treated and untreated adopted girls, found that final height compared with initial PAH was on average more impaired in untreated (initial PAH 158.5, final height 154.3 cm) than in treated girls (initial PAH 152.8 cm, final height 152.0 cm). The diminished growth potential after discontinuation of treatment with GnRH agonist might hamper the potential beneficial effect. Therefore, the addition of growth hormone during treatment with GnRH agonist has been investigated by some groups. Mul *et al.* (13) evaluated adopted girls treated with GnRH agonists alone or in combination with growth hormone. It was shown that in the growth hormone-treated group, PAH during treatment increased significantly more than in the group treated with GnRH agonists alone, but data on final height achievement were not (yet) shown. An Italian group reported that the addition of growth hormone improved final height as well, but this study was not randomized (20).

The relatively low mean final height in the adopted girls might result from a subgroup of children with normally timed puberty (i.e. >8 years) who were treated because of impaired adult height prognosis. Because the response pattern during treatment for the three adopted girls where puberty started after the age of 8 years was similar to the girls where puberty started before 8 years, these three children were included in the analysis. For the interpretation of final height,

subgroup analysis showed that adopted children with puberty starting before 8 years reached a final height of 157.7 compared with 151.8 cm in adopted children with puberty starting after 8 years.

Before, during and after treatment, the treated girls in both groups were heavier than their peers. The method used standardized height for weight. This calculation gives, in our opinion, a reliable approach with which to value weight in relation to height. The WFH index (8) is often not applicable for children with precocious puberty, because their height is too tall to fit into the appropriate age group. No matter what method is used, careful interpretation of the results is needed. Children with precocious puberty have oestrogen-dependent pubertal weight, while they are compared with WFH standards for prepubertal girls. This may explain, in part, the overweight seen in the majority of patients, which is consistent with other reports (15, 21). This would imply that adult weight should be normal. In fact, the body mass index at the end of treatment is within normal limits.

In 11 girls (five idiopathic and six adopted), progression of puberty led to the stimulation of the endometrium, resulting in menses before treatment or withdrawal bleeding during the first weeks of treatment. This occurred relatively more in adopted girls, which can be explained by the fact they were, in general, older. After the end of treatment, menses (re)occurred at the age of 12.7 and 12.8 years respectively, on average about 1 year after treatment had been stopped. This is comparable with treated girls with idiopathic precocious puberty in The Netherlands (mean age 12.3 years, 1.1 year after treatment) (15). However, it is still earlier than in the general Dutch population (mean age 13.2 years) and later than untreated adopted girls in Sweden (mean age 11.6 years) (22) and untreated adopted girls in The Netherlands (mean age 12.0 years) (3). In the latter study, early menarche was related to late age at arrival and fast catch-up growth.

In conclusion, we have compared the response to GnRH agonist treatment in girls with idiopathic precocious puberty and adopted girls. Despite the difference with respect to timing of puberty and duration of treatment, the response to treatment was in many aspects similar. The girls with idiopathic precocious puberty reached a final height comparable to the mean height of the Dutch population. In contrast, adopted girls reached a final height of about -2 S.D., which is comparable to the mean final height in their native country.

Acknowledgements

MA van't Hof is greatly acknowledged for his contribution to the statistical analysis of the data.

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Received 23 November 2001

Accepted 8 July 2002