Final Adult Height in "Early Normal Pubertal Girls" Treated with Gonadotropin Releasing Hormone Agonists

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Abstract

Gonadotropin releasing hormone (GnRH) agonist has been used worldwide for the treatment of central precocious puberty. However, the results on final adult height (FAH) are discrepant in various studies especially in girls with normal early puberty. Fourteen girls with normal early puberty who were treated with depot GnRH agonists 3.75 mg intramuscular (IM) monthly for a mean period of 1.5 ± 0.4 yr were retrospectively studied. The chronological age and bone age at the beginning of treatment were 9.9 ± 0.7 yr and 12.6 ± 0.9 yr, respectively. When the treatment was stopped, all the girls were followed-up until they reached their final adult heights. The results showed that the mean FAH was 154.0 ± 6.9 cm, which was not significantly different from the predicted adult height (PAH) at start of treatment, 153.1 ± 6.2 m. All the girls were divided into 2 groups. Group A was girls who had FAH-PAH at the start of treatment ≥ 1.5 cm and group B, FAH-PAH at the start of treatment < 1.5 cm. The authors found that only the duration of treatment was different between these 2 groups, 1.7 ± 0.3 yr in group A and 1.3 ± 0.3 yr in group B ($p = 0.015$).

In conclusion, GnRH agonist cannot improve the final height outcome in girls with normal early puberty. However, a longer period of treatment may improve the height prognosis.

Key word : Early Normal Puberty, GnRH Agonist, Final Adult Height

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Central precocious puberty (CPP) or true precocious puberty (TPP) is due to a premature secretion of gonadotrophin. This phenomenon can accelerate the growth and cause a premature closure of the epiphyseal plates. Eventually, these girls become short adults. In the past, treatment with a progestational agent could arrest or regress the signs of puberty but had no beneficial effects to improve the final adult height[1]. At present, depot GnRH agonist is the treatment of choice in CPP because it has a direct effect on gonadotrophin secretion. GnRH agonist can block the pituitary-gonadal axis and slow down the bone age progression and preserve the growth potential. Many previous studies showed the beneficial effects of depot GnRH agonists on final adult height especially in girls with onset of disease before 5-6 years of age[2-5]. However, little is known about the effect of depot GnRH agonist on the final height in girls with "early normal puberty". The aim of this study was to report the final adult height in early normal pubertal girls treated with depot GnRH agonists.

MATERIAL AND METHOD

Fourteen early normal pubertal girls treated with depot GnRH agonist were retrospectively reviewed. "Early normal puberty" or "advanced puberty" was defined in girls with onset of breast development around the age of 8 years and/ or menarche between the age of 9 $^1/_2$ and 10 $^1/_2$ years old. The treatment was started because of the parents' concern about the final height outcome. Luteinizing hormone releasing hormone (LHRH) test was performed on all the girls and the results showed the pubertal response of peak LH > 10 mU/L and LH/FSH > 1. Magnetic resonance imagine (MRI) was performed to exclude pathological causes. Depot GnRH agonists were given intramuscularly every 4 weeks. Treatment was stopped when parents were satisfied with the predicted adult height (PAH). When the treatment was stopped, all the girls were followed-up until they reached their final adult height (FAH). The FAH was defined when the bone age was more than 14 years and the height velocity less than 1 cm per year. FAH was compared with PAH at the start and end of treatment. PAH was estimated by the method of Bayley and Pinneau. The results are shown as mean ± SD. Non parametric analysis was performed using the Statistical Package for Social Sciences (SPSS), Wilcoxon signed rank test in two related samples and Mann-Whitney U test in two-independent samples. $P < 0.05$ was considered significant.

RESULTS

Fourteen girls had a mean chronological age and a mean bone age of 9.9 ± 0.7 years and 12.6 ± 0.9 years, respectively, at start of treatment. Therefore, the PAH at the start of treatment was 153.1 ± 6.2 cm which was lower, but not significant, than the mid parental height of 154.4 ± 4.4 cm. Treatment with depot GnRH agonist 3.75 mg intramuscular every 1 month was given to all the girls with the mean duration of 1.5 ± 0.4 years (range 1-2 years). When the treatment was stopped, the bone age was 13.0 ± 0.8 years and the PAH was 157.3 ± 7.3 cm which was significantly higher than when the treatment was started (153.1 ± 6.2 cm) ($p = 0.025$). After the treatment was stopped, all the girls were followed-up until they reached the FAH according to the mentioned criteria. The mean FAH was 154.0 ± 6.9 cm which was not significantly different from the PAH at the start of treatment.

All the girls were divided into 2 groups according to their height gain. Height gain was defined as a difference between FAH and PAH at the start of treatment. Group A ($n = 8$), the height gain was equal to or more than 1.5 cm. Group B ($n = 6$), the height gain was less than 1.5 cm. The data of these two groups is shown in Table 1. The result showed that only the duration of treatment was significantly different between these two groups, 1.7 ± 0.3 year in group A and 1.3 ± 0.3 year in group B ($p = 0.015$).

DISCUSSION

GnRH agonist has been accepted as the treatment of choice in girls with CPP. This drug induces a desensitization of the pituitary to hypothalamic LHRH resulting in a decrease of gonadal sex hormone. Therefore, the fusion of the epiphyseal plates is delayed and this allows a longer period of growth and, eventually, the final height increases. In contrast, treatment with progestational agents could suppress or regress the signs of puberty but the final height was not improved. Many previous studies demonstrated the effectiveness of depot GnRH agonist to improve the FAH in girls with CPP especially if the onset of disease and the treatment was started before 5-6 years of age[2-5]. Although FAH was greater than that in

Table 1. Clinical data of the 2 groups.

	Group A (n = 8)	Group B (n = 6)	P-value
CA (yr)	9.9 ± 0.6	9.9 ± 0.9	1.0
BA (yr)	12.8 ± 0.8	12.3 ± 1.0	0.28
Mid parental height (cm)	153.1 ± 4.6	156.4 ± 3.5	0.19
PAH start treatment (cm)	152.1 ± 5.5	154.7 ± 7.4	0.49
PAH stop treatment (cm)	157.6 ± 6.8	156.8 ± 8.9	0.77
FAH (cm)	155.4 ± 7.6	152.0 ± 5.9	0.4
Duration of Rx (yr)	1.7 ± 0.3	1.3 ± 0.3	0.015

CA = chronological age, BA = bone age, PAH = predicted adult height, FAH = final adult height, Rx = treatment

the control group and in the girls treated with progestational agents and was also greater than the initial PAH, the FAH was significantly less than the target heights. The authors' previous study also demonstrated the improvement of PAH in girls with CPP and treated with GnRH agonist, however, the FAH was not promising[6]. Early normal puberty is the most frequent variant in the spectrum of central precocious puberty and, nowadays, it is a common problem in pediatric practice. This condition is defined when a pubertal onset is only mildly in advance of normal. Treatment with depot GnRH agonists in early normal pubertal girls in order to delay the epiphyseal fusion and improve the adult stature has been demonstrated in a few studies. However, the overall results did not support a beneficial effect of GnRH agonist to improve the final height[3,7-9]. Bouvattier C et al showed the final adult height was 1.5 cm higher in treated group compared with the control group[10]. The present study also showed the same results although the duration of treatment was shorter than in other studies. However, the height gain was improved if the duration of treatment was prolonged as demonstrated in group B. This was supported by Nelly et al who reported that decreased bone age standard deviation score and improvement of PAH would occur in the second year of treatment with GnRH agonist[4]. In the present study, only auxological results were evaluated. There are other factors that might justify the treatment and should be considered such as psychological or behavior problems[11]. In conclusion, treatment with GnRH agonist in normal early pubertal girls cannot improve FAH. Therefore, the decision to start depot GnRH agonist in this condition should be carefully reviewed in order to avoid "overprescription" of this drug and the parents should be counseled regarding the final height outcome.

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ความสูงเมื่อโตเป็นผู้ใหญ่ในเด็กผู้หญิงที่เป็นสาวเร็วปกติและได้รับการรักษาด้วย GnRH agonist

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GnRH agonist เป็นยาที่นำมาใช้กันอย่างแพร่หลายในการรักษาเด็กผู้หญิงที่มีปัญหาเป็นสาวก่อนวัยอันควร (precocious puberty) การศึกษาที่ผ่านมาพบว่าผลของการรักษาในด้านความสูงสุดท้ายเมื่อโตเป็นผู้ใหญ่นั้นได้ผลแตกต่างกันโดยเฉพาะอย่างยิ่งในเด็กผู้หญิงที่มีภาวะเป็นสาวเร็วปกติ (early normal puberty) การศึกษานี้จึงได้ทำการศึกษาแบบย้อนหลังเพื่อดูความสูงสุดท้ายเมื่อโตเป็นผู้ใหญ่ในเด็กหญิงที่เป็นสาวเร็วปกติ และได้รับการรักษาด้วย GnRH agonist ขนาด 3.75 มิลลิกรัม ฉีดเข้ากล้ามเนื้อเดือนละ 1 ครั้ง เป็นระยะเวลาเฉลี่ย 1.5 ± 0.4 ปี พบว่าเด็กผู้หญิงจำนวนทั้งสิ้น 14 คน มีอายุจริงและอายุกระดูกเมื่อเริ่มให้การรักษาเท่ากับ 9.9 ± 0.7 และ 12.6 ± 0.9 ปี ตามลำดับ หลังจากหยุดการรักษาได้มีการติดตามความสูงเด็กเหล่านี้จนเด็กเหล่านี้โตเป็นผู้ใหญ่และได้ความสูงสุดท้ายเท่ากับ 154.0 ± 6.9 เซนติเมตร ซึ่งไม่แตกต่างกับความสูงที่คาดเดาจากการคำนวณเมื่อเริ่มต้นให้การรักษาซึ่งมีค่าเท่ากับ 153.1 ± 6.2 เซนติเมตร เมื่อแบ่งเด็กออกเป็น 2 กลุ่ม คือกลุ่ม A ซึ่งมีความแตกต่างระหว่างความสูงสุดท้ายเมื่อเป็นผู้ใหญ่กับความสูงที่คาดเดาจากการคำนวณเมื่อเริ่มต้นรักษามากกว่าหรือเท่ากับ 1.5 เซนติเมตร และ กลุ่ม B ซึ่งมีความแตกต่างดังกล่าวน้อยกว่า 1.5 เซนติเมตร พบว่า มีเพียงระยะเวลาของการรักษาเท่านั้นที่แตกต่างกันใน2 กลุ่มนี้ คือ กลุ่ม A มีระยะเวลารักษา 1.7 ± 0.3 ปี และ กลุ่ม B มีระยะเวลารักษา 1.3 ± 0.3 ปี (p = 0.015) จากการศึกษาครั้งนี้สรุปได้ว่า GnRH agonist ไม่มีประโยชน์ในการเพิ่มความสูงสุดท้ายเมื่อโตเป็นผู้ใหญ่ในเด็กหญิงที่เป็นสาวเร็วปกติ แต่การรักษาที่นานขึ้นอาจทำให้ผลการรักษาดีขึ้นไปกว่านี้

คำสำคัญ : เป็นสารเร็วปกติ, จี เอ็น อา เอช อะโกนิสต์, ความสูงสุดท้ายเมื่อโตเป็นผู้ใหญ่

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