Original Article

The Beneficial Effect of Chinese Herb Medicine for Precocious Puberty Patients Receiving Gonadotropin-Releasing Hormone Homolog Therapy

Wan-Jung Lin[1,†], Chin-Chuan Tsai[1,3,†], Li-Min Chen[2], Jung-Sheng Yu[1,3], Chun-Hwa Yang[3], San-Nan Yang[2,4,]*

Objective: Precocious puberty is an endocrine disease in children. Precocious puberty is understood as the second sexual development of a boy before the age of nine or before girl is eight years old, or that the girl's menarche occurs before the age of ten. The disease will eventually lead to the epiphyseal plate to close beforehand, resulting in a shorter height in adulthood than normal persons. Currently, such patients usually conventionally receive the gonadotropin-releasing hormone homolog (GnRH-a) treatment, in the absence of other effective adjunctive therapy. This study was designed to determine whether Chinese herb medicine may serve as a beneficial adjunctive therapy for the central precocious puberty patients receiving conventional GnRH-a treatment.

Methods: A total of sixteen subjects (2 boys; 14 girls) without any other systemic or congenital diseases were diagnosed with central precocious puberty were treated with conventional GnRH-a protocol in the absence or presence of Chinese medicine supplementation for a maximal 24-months course. During the period of such combined treatment protocol, the bone age, serum sex hormone level, and Tanner maturation score were evaluated at specific time points.

Results: This study revealed that a two-year adjunctive protocol of Chinese herb medicine significantly promoted the clinical manifestations in central precocious puberty patients, including the development of breast maturation, genital itching and vaginal discharge, bone age, and serum hormone level (FSH 2.91 mIU/mL, LH 0.37 mIU/mL, Estradiol (E2) < 10 pg/mL, T4 7.94 μg/dL, TSH 2.48 uIU/mL). In addition, the life quality score were significantly improved in the central precocious puberty patients receiving Chinese herb medicine.

Conclusions: The results suggest that a beneficial effect of the Chinese herb medicine may serve as an effective adjunctive therapy for the central precocious puberty patients receiving conventional GnRH-a treatment.

Key words: precocious puberty, bone age, Chinese medicine, gonadotropin-releasing hormone

From the [1]Department of Chinese Medicine, E-Da Hospital, and [2]Departments of Pediatrics, E-Da Hospital, and [3]School of Chinese Medicine for Post Baccalaureate, I-Shou University, and [4]School of Medicine, College of Medicine, I-Shou University, Kaohsiung, Taiwan

(† signifies equal contribution compared to the first author)

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* Address reprint request and correspondence to: San-Nan Yang, College of Medicine, I-Shou University, No.8, Yida Road, Jiaosu Village, Yanchao District, Kaohsiung City 82445, Taiwan.

Tel:+886-07-6150011 ext. 252345, E-mail: y520729@gmail.com

Introduction

Precocious puberty is defined as the second sexual development of a girl before the age of eight or before the boy is nine years old or that the menarche of the girl occurs before the age of ten.[1,2] The incidence rate of precocious puberty has been widely reported by countries. Due to the influence of environmental endocrine disruptors, the prevalence of precocious puberty is increasing year by year. Apart from ethnic influences, precocious puberty is also common among girls or obese children.[3,4,5]

According to the different causes of the disease, precocious puberty can be allocated into central precocious puberty and peripheral precocity. Central precocious puberty (CPP), also known as true precocious puberty or gonadotropin-dependent precocious puberty, is due to premature activation of the hypothalamic-pituitary-gonadal axis, resulting in the secretion of gonadotropin-releasing hormone (GnRH), leading to gonads hormone hypersecretion.[6] Up to 90% of girls with central precocious puberty are idiopathic. Other possible causes include genetic mutations, central nervous system tumors, trauma, inflammatory diseases, hydrocephalus, or exposure to excessive hormonal stimuli.[7] The causes resulting in peripheral precocious puberty, also known as non-sexual reductive-dependent precocious puberty are germ cell tumors, ovarian cysts, ovarian tumors, sputum stromal cell tumors, and adrenal tumors which leads to an excessive secretion of estrogen from the ovaries, testes, or adrenal glands.[8,9,10]

Precocious puberty causes an increase in growth hormone leading to accelerated bone age development, which ultimately causes the epiphyseal plate to close in advance. Thus, such sick children manifested to be taller.[11] Currently, modern western medicine treatment of precocious puberty in addition to the treatment of local causes, for children with CPP without specific causes, usually given gonadotropin-

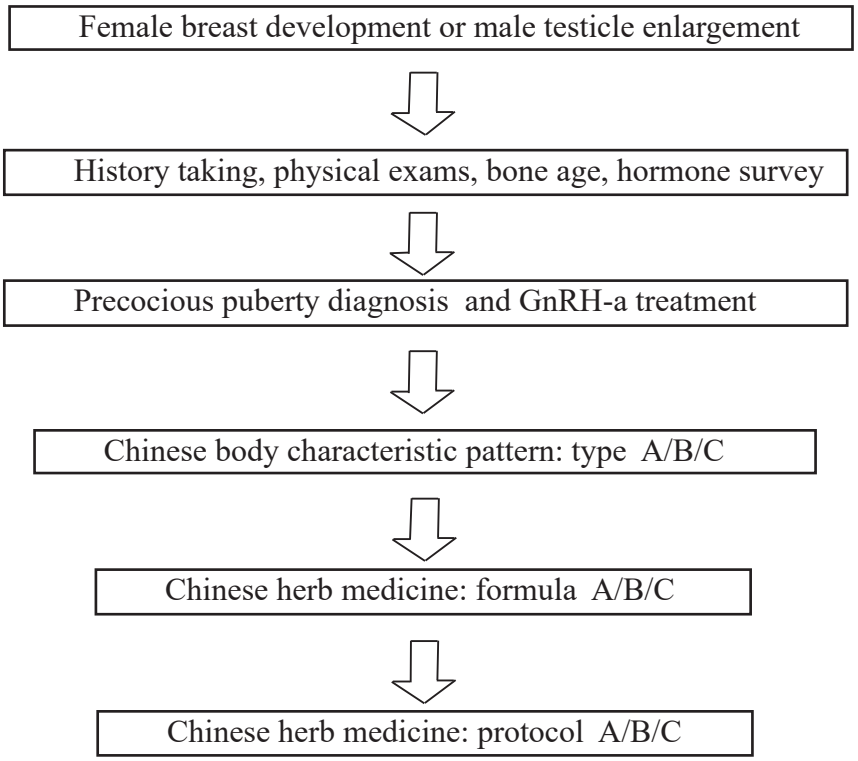

Fig. 1 Schematic illustration of study design and protocol. A total of sixteen subjects (2 boys; 14 girls) without any other systemic or congenital diseases were diagnosed with central precocious puberty and treated with conventional GnRH-a treatment in the absence or presence of adjunctive therapy of Chinese herb medicine.

releasing hormone homolog (GnRH-a, trade name: Leuplin™) treatment.[12] Recently, the use of complementary and alternative medicine to treat CPP has increased in Asia.[9,11,12] Chinese herbal medicines have been used to delay pubertal development and promote growth in patients with CPP.[13-17] Thus, this study was designed to determine whether the protocol of Chinese herb medicine may serve as a beneficial adjunctive therapy for CPP patients receiving conventional GnRH-a treatment.

Methods

This study was approved by the IRB of E-Da Hospital, Taiwan, and all patients participating in this trial were regularly followed at Department of Pediatrics and Department of Chinese Medicine of E-Da Hospital, Taiwan. A total of sixteen subjects (2 boys plus 14 girls) without any other systemic or congenital diseases were diagnosed with CPP were treated with conventional GnRH-a protocol in the absence or presence of Chinese herb medicine therapy, as described in Figure 1 and 2. During a two-year protocol of Chinese herb medicine treatment, this study has compiled the track record of outpatient clinics. The follow-up evaluation, including Tanner Maturation Score, body length, and biochemical profile were examined as the designed time points. All data in the present study are presented as mean ± standard error of mean (SEM). Statistical differences were determined by either Student's t test, one-way analysis of variance, or two-way analysis of variance with the Bonferroni's t-test for post-hoc multiple comparisons. Statistical significance was determined at $p < 0.05$.

Results

To determine whether an adjunctive therapy of Chinese herb medicine with GnRH-a treatment led to beneficial effects in enrolled subjects, the life quality score (Fig. 3) was applied to analyze the overall manifestations of the subjects in this study. As shown in Figure 4 in 15 weeks treatment, there was no significant difference of the maturation score between the GnRH-a treatment alone group and the GnRH-a plus Chinese medicine group during such early combined treatment protocol. In contrast, the maturation scores of the later treatment , i.e., 17 weeks were persistently higher in the GnRH-a plus Chinese medicine group, as compared to the GnRH-a treatment

Pattern	Firmula	Protocol
(Pattern A) Kidney yin deficiency	**(Formula A)** Zhi Bai Di Huang Wan	**(Protocol A)** Rehmann Radix Corni Fructus, Dioscoreae Rhizoma, Poria Moutan Cortex, Alismatis Rhizoma, Anemarrhenae Rhizoma Phellodendri Amurensis Cortex
(Pattern B) Depressed live *qi* transforming into fire	**(Formula B)** Jia Wei Xiao Yao San	**(Protocol B)** Angelicae Sinensis Radix, Poria, Gard eniae Fructus, Menthae Haplocalycis Herba, Paeoniao Radix Alba, Bupleuri Radix, Glycyrrhizae Radix et Rhizoma, Atractylodis Macrocephalae Rhizoma, Moutan Cortex, Zingiberis Rhizoma Recens
(Pattern C) Binding of phlegm and heat	**(Formula C)** Er Chen Tang and Er Miao San	**(Protocol C)** Citri Grandis Exocarpium, Poria, Glycyrrhizae Radix et Rhizoma, Pdellodendri Amurensis Cortex, Atractylodis Rhizoma, Zingiberis Rhizoma Recens, Pinelliae Rhizoma

Fig. 2 Three formula protocols of Chinese herb medicine based on referring Chinese body characteristic pattern of the enrolled subjects.

Mean episodes/week in this month	Never Score 4	1-2 times 3	3-4 times 2	5-7 times and more 1
Clinical manifestations				
Sweating in night time				
Thirsty in night time				
Bitterness in night time				
Irritability in night time				
Facial flushing in night time				
Breast pain in night time				
Subcostal pain in night time				
Fatigue				
Whole body flushing in night time				
Cough in night time				
Vaginal discharge				
Diarrhea				

Fig. 3 Application of life quality scores for the analysis of clinical manifestations in the enrolled subjects in this study.

alone group. Furthermore, the mean maturation score in the first week in the GnRH-a treatment group and the GnRH-a plus Chinese medicine group was 43.0 and 42.3, respectively ($p > 0.05$, n = 16). Following a 25-week treatment course, the mean maturation score in the GnRH-a treatment alone group and the GnRH-a plus Chinese medicine group was 45.0 and 47.5, respectively ($p < 0.05$, n = 16).

To determine whether the bone age was changed by an adjunctive Chinese herb medicine in CPP patients receiving GnRH-a, the left-hand X-ray imaging was taken. As shown in Figure 5, after one year therapy of Chinese herb medicine, the bone age was significantly promoted for a representative CPP patient. In addition, the serum hormone level also revealed as follows: FSH 2.91 mIU/mL, LH 0.37 mIU/mL, Estradiol (E2) < 10 pg/mL, T4 7.94 μg/dL, TSH 2.48 uIU/mL.

Discussion

Here in this study, we have suggested that an adjunctive Chinese herb medicine may contribute a beneficial role for CPP patients receiving gonadotropin-releasing hormone homolog therapy, including the promotion of bone age, increase of maturation score, and recovery of sex hormone level. The clinical manifestations of precocious puberty were all relieved.

Precocious puberty is a common endocrine disease in children. It is defined as the second sexual development of a girl before the age of eight or before the boy is nine years old, or that the menarche of a girl occurs before the age of ten. According to the cause, it can be divided into central precocious puberty and peripheral precocious puberty; the disease will eventually cause the bones to close earlier, resulting in a shorter height in adulthood than normal people. Western medicine treatment is mainly gonadotropin-releasing hormone homolog (GnRH-a, trade name: Leuplin, Liu Bolin long-acting injection). In addition to requiring detailed medical history and physical examination, clinically precocious children need a combination of laboratory and imaging studies to make the most accurate assessment.[11,18] The medical history inquiry should include the time and condition of the development of the second sexuality, and the second sexual development time of the parents or siblings; in addition, the symptoms of central nervous system diseases such as headache, epilepsy, behavior or visual changes should be noticed, as well as a possibility of exposure to environmental hormones. In general, physical examinations for such CPP patients should be carefully performed, including height, weight, growth rate (cm/year) and

secondary sexual development assessment.[3-5,19] More importantly, the maturation score based on Tanner's staging is clinically used as a major criterion for assessing the development of secondary sexual characteristic, including pubic hair development and development of female breast or male genitalia.[4]

In addition to physical examinations for such CPP patients, the imaging examination mainly focuses on the X-ray film of the left wrist. It is estimated whether the current age of the bone is consistent with the actual age based on the growth and development of the wrist bone and the degree of healing of the epiphyseal plate.[11] In general, laboratory tests should be performed as follows: serum concentrations of luteinizing hormone (LH), follicle-stimulating hormone (FSH), estradiol, testosterone, and other hormonal dysfunction.[8,9]

In this study, on the basis of traditional Chinese body characteristic patterns A, B, and C, Chinese herb medicine for precocious puberty treatment were categorized into three therapeutic formula protocols A, B, and C, respectively. It is a transitional period in which children are transferred to adults. In addition to secondary sexual development and gonad maturation, they have fertility and are accompanied by cognitive, psychological, and neurobehavioral changes.[11] Some studies have also pointed out that the combination of traditional Chinese and Western medicine for the treatment of precocious puberty may be better than Western medicine alone.[13-17] Adolescence is between childhood and adulthood and is a transitional period in which children become adults.[15,20,21] Recently, The *nine-storey tower* is also known as Ocimum basilicum. It has a medicinal taste, sweetness and warmness. It enters the spleen, lung, stomach and large intestine. It has been hypothesized that the wind may solve the table and lead to a humidification and medium, *qi* and blood circulation, detoxification and swelling. Although there is no relevant empirical study on the vertical growth of the nine-story tower and bone, the nine-layer tower also increases osteoblast activity by binding to estrogen receptors.[14,17] For instance, *Centella asiatica* is a commonly used Chinese herbal medicine in Taiwan, also known as *Leigonggen*

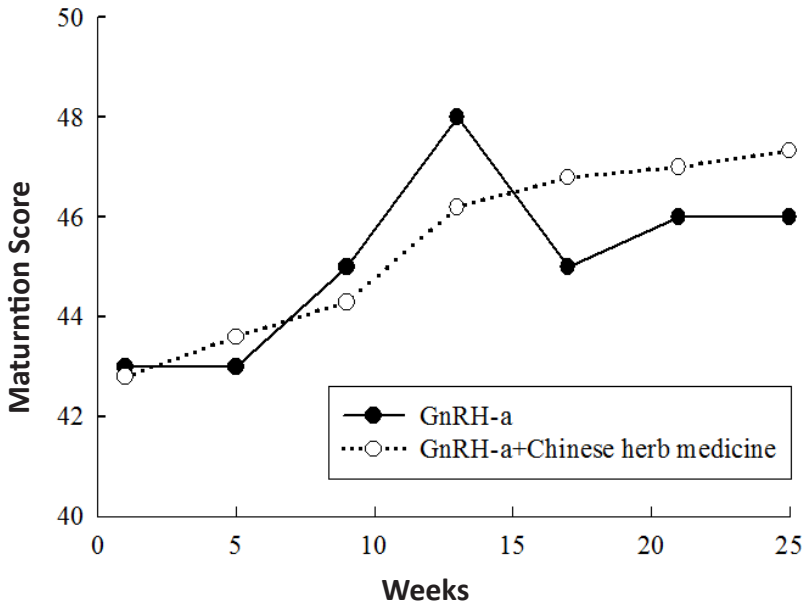

Fig. 4 Comparisons in maturation score for the subjects receiving conventional GnRH-a therapy in the presence or absence of Chinese herb medicine protocol. After a 24-week period of adjunctive therapy of Chinese herb medicine, the long-term maturation score, indicating by the asterisks, in the subjects with GnRH-a plus Chinese herb medicine were significantly higher than the subjects GnRH-a alone.

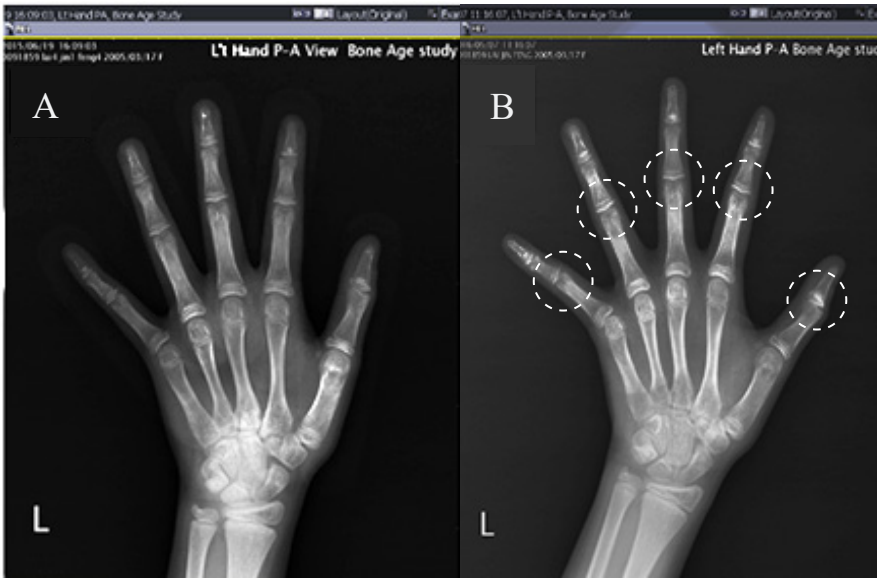

Fig. 5 The left-hand bone age analysis revealing by X-ray imaging for a representative patient receiving conventional GnRH-a therapy before and after Chinese herb medicine protocol. The bone age imaging was taken for the subject at the age of ten years and three months (A) and eleven years and three months (B) There was a significant promotion in bone age characteristic study as indicated by the white dashed circles.

or *Centella asiatica*. Chinese medicine believes that its medicinal taste is bitter, spicy, and cold. The effect is clearing heat and dampness, promoting blood circulation and relieving blood, detoxification and swelling. Modern studies of *sassafras* extracts have shown anti-inflammatory, anti-allergic and anti-itching effects.[14,17] In addition, *Setaria viridis*, also known as *Taiwan ginseng*, is sweet and warm, functionally beneficial to water, spleen, insecticide, *qi*, and help children develop. It treats all stomach pains, labor heat, hemoptysis, loss of true gas, dysplasia in children.

According to the current modern pharmacological research, the pharmacological machine of commonly used Chinese herbal medicine can be divided into the promotion of longitudinal growth of bone and the promotion of bone quality. The commonly used Chinese herbal medicines such as nine-layer tower, clam grass, 10,000-point gold and foxtail are not relevant in Taiwan. An empirical study on the promotion of longitudinal growth of bone,[14,17,20-23] which also provides a new research direction, is waiting for future scholars and experts to confirm its pharmacological mechanism, hoping to explore the relevant treatment methods through the discussion of Chinese medicine literature.

In Asian countries, Chinese herbal medicine is a form of complementary medicine that has been applied to CPP patients.[14,17] In recent studies, Chinese herbal medicines have been studied as both formulas and as single agents. All formulations of herbal medicine, such as decoctions, tablets, capsules, pills, powders, and extracts, will be considered for inclusion in this review. Because of the increased incidence of CPP and treatment limitations, there is a critical and urgent need to identify and develop safe, complementary and alternative treatments for children with CPP.

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