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Effect of Dietary Intervention Combined with Anshen Ziyin Xiehuo Prescription on Children with Idiopathic Central Precocious Puberty

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Keywords

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Abstract

Objective: This study explores the effect of dietary intervention combined with Anshen Ziyin Xiehuo prescription on children with idiopathic central precocious puberty. **Methods:** Forty-seven children treated with dietary intervention combined with Anshen Ziyin Xiehuo prescription in our hospital from January 2022 to December 2022 were allocated into dietary group, and 47 children treated with Anshen Ziyin Xiehuo prescription during the same period were assigned into control group. Treatment was performed for 6 months. The clinical effects in the two groups were compared, and the changes of bone age, bone metabolism, breast development, and ovarian function before and after treatment were evaluated and compared. **Results:** The total effective rate of clinical efficacy in the dietary group was significantly higher than that in the control group ($p < 0.05$). After treatment, bone age, Tanner breast staging score, and levels of estrogen, luteinizing hormone, and follicle-stimulating hormone in the two groups were decreased, and these in the dietary group were lower than those in the control group ($p < 0.05$). The levels of total procollagen type I amino-terminal propeptide and beta-C-terminal telopeptide of type I collagen were increased in two groups, and the levels in the dietary group were higher than those in the control group ($p < 0.05$). During treatment, no adverse reactions such as hyperhidrosis, back pain, dizziness, and dry mouth were found in both groups. **Conclusion:** Dietary intervention combined with Anshen Ziyin Xiehuo prescription has good clinical efficacy in the treatment of idiopathic central precocious puberty, which can slow down the growth of bone age and inhibit bone metabolism as well as development of breast and ovarian, with good safety.

1 Introduction

Idiopathic central precocious puberty is an endocrine disease commonly seen in girls, which is caused by premature activation of the hypothalamic-pituitary-gonadal axis, and clinically manifested by abnormal development of the first and second sex characteristics [1,2]. If left untreated, patients with idiopathic central precocious puberty may also experience early epiphyseal fusion, and in severe cases, their height potential will be compromised [3]. Gonadotropin-releasing hormone (GnRH) agonists are the gold-standard treatment, it can inhibit the function of the hypothalamic-pituitary-gonadal axis, thereby inhibiting the secretion of sex hormones [1]. However, the treatment cycle is long, some parents are worried about its potential side effects, if long-term use of hormone drugs, easy to produce adverse reactions, and can cause drug dependence, long-term efficacy and prognosis are limited.

In traditional Chinese medicine, precocious puberty of girls belongs to the category of “areolar nodule” and “advanced menstruation”, and its etiology lies in the hyperactivity of fire due to yin deficiency and depression of the liver generating pathogenic fire. Hence, its treatment should be based on nourishing the yin, suppressing hyperactive yang, and purging away the ministerial fire [4]. A systematic review and meta-analysis found that herbal medicine can effectively reduce serum estrogen (E2), luteinizing hormone (LH) level and bone age, and it has a significant effect on the treatment of idiopathic central precocious puberty [5]. In addition, it has been reported that Zhi-Bai-Di-Huang-Wan plus Mai-Ya could be as a commonly accepted TCM prescription for idiopathic precocious puberty [6]. As a formula that nourishes yin, purges the pathogenic fire, calms the nerves, and benefits sleep, Anshen Ziyin Xiehuo Prescription has the effect of delaying breast and pelvic development and lowering the levels of sex hormones. Chen et al. have proved that Anshen Ziyin Xiehuo Prescription has good efficacy in children with idiopathic central precocious puberty [7]. In addition, a foreign study exploring the dietary habits of girls with precocious puberty showed that precocious puberty in girls may be related to the factors such as eating too fast, disrupted eating schedules, and excessive intake of high-calorie foods, so dietary interventions need to be combined in the treatment of patients with idiopathic central precocious puberty [8]. Yang et al. have demonstrated that dietary intervention is effective in slowing down the growth and development of children with idiopathic central precocious puberty [9]. At present, the clinical treatment of children with idiopathic central precocious puberty mainly focuses on inhibiting the development of sex characteristics and bone metabolism.

Based on these, the present study combined dietary intervention with Anshen Ziyin Xiehuo prescription in the treatment of idiopathic central precocious puberty to observe their effects on bone age (BA), bone metabolism, breast development, and ovarian function, with the aim of providing more bases and references for the clinical treatment of this disease.

2 Materials and methods

2.1 General data

Forty-seven children treated with dietary intervention combined with Anshen Ziyin Xiehuo prescription in our hospital from January 2022 to December 2022 were allocated into dietary group, and 47 children treated with Anshen Ziyin Xiehuo prescription during the same period were divided into control group. General information including age, BA, height, weight, and Tanner breast staging score was collected for both groups.

2.2 Inclusion and exclusion criteria

2.2.1 Inclusion criteria

(1) Patients met the diagnostic criteria for idiopathic central precocious puberty in the *Consensus on the Diagnosis and Treatment of Idiopathic Central Precocious Puberty (2015)* [10]. (2) Patients met the diagnostic criteria for precocious puberty in *Guidelines for Clinical Diagnosis and Treatment of Pediatric Precocious Puberty in Chinese Medicine (Revised)* [11]. (3) Patients were diagnosed by ultrasound, BA, and sex hormone tests. (4) Patients aged 5-12 years. (5) Patients were diagnosed for the first time and had no history of systemic therapy.

2.2.2 Exclusion criteria

(1) Patients with secondary central precocious puberty. (2) Patients with first menstruation or simple early breast development. (3) Patients with the diseases affecting their growth and development such as hyperthyroidism and severe malnutrition. (4) Patients with long-term passive use of hormone drugs or food. (5) Patients with central nervous system tumors. (6) Patients with cardiovascular, cerebrovascular, or hematopoietic system diseases. (7) Patients with mental disorders and poor treatment compliance. (8) Patients with severe cardiac, hepatic, pulmonary, and renal insufficiencies. (9) People who were allergic to the drugs in this study.

2.3 Methods

2.3.1 Control group

Patients orally took Anshen Ziyin Xiehuo Prescription (formula: 9 g *Rehmannia glutinosa*; 10 g *Poria*; 10 g *Anemarrhenae Rhizoma*; 10 g *Polygalae Radix*; 10 g *Fructus Hordei Germinatus*; 9 g *Ziziphi Spinosae Semen*; 10 g *Moutan Cortex*; 10 g *Paeoniae Radix Alba*; 10 g *Carapax Testudinis*; 9 g *Phellodendron amurense*, 10 g *Alismatis Rhizoma*, and 9 g *Platycladi Semen*). Anshen Ziyin Xiehuo Prescription was decocted in water to 400 mL, and taken by patients in the morning and evening, 200 mL/time and 1 dose/day. Treatment was performed for 6 months.

2.3.2 Dietary group

Based on the treatment in control group, patients in dietary group were treated with dietary intervention. Diet was developed according to the website (https://nlc.chinanutri.cn/fq/), and patients' family members were instructed to pay attention to dietary diversification, balanced nutrition, and supplementation of grains and fresh fruits and vegetables. Also, they were advised to choose seasonal fresh vegetables rather than anti-seasonal vegetables as much as possible, and take at least 250 g carbohydrates, 25 g dietary fibre, 20 g dietary fat, and 400 U vitamin D every day, instead of foods that are high in estrogen such as dairy products, soy products, and honey, desserts, fried food, poultry, and meat, as well as tropical fruits such as durian and mango. Treatment was performed for 6 months.

2.4 Observation indicators

2.4.1 Clinical efficacy

The evaluation criteria of efficacy referred to *Consensus on the Diagnosis and Treatment of Idiopathic Central Precocious Puberty* (2015) [10] and *Recommendations for the Diagnosis and Treatment of Central (true) Precocious Puberty* [12]. Criteria were listed below. Cured: complete disappearance of symptoms and signs, reduction of breast volume to prepuberty, shrinkage of ovarian and uterine volume to normal, lower growth of BA than age, and serum hormone level in normal range; significantly effective: obvious improvement of symptoms and signs, reduction of breasts, ovary, and uterus volume, the same growth of BA and age, and apparent decrease of serum hormone level; effective: improvement of symptoms and signs, reduction of breast, ovary and uterus volume, the nearly same growth of BA and age,

and decrease of serum hormone level; ineffective: failure to meet the above criteria or even aggravation of disease. The total clinical effective rate = (cured + significantly effective + effective) cases / total cases × 100%.

2.4.2 BA

Before and after 6 months of treatment, BA films of the left hand in both groups of patients were taken using a BA meter, and the ratio of BA to chronological age (CA) was calculated.

2.4.3 Bone metabolism and ovarian function

Before and after 6 months of treatment, 5 mL of fasting peripheral venous blood was drawn from the patients of both groups, left at room temperature for 30-60 min, and centrifuged at 3,000 r/min for 10 min. Later, the serum was separated and stored at -20 ℃ for measurement. Total procollagen type I amino-terminal propeptide (tPINP), beta-C-terminal telopeptide of type 1 collagen (β-CTX), estrogen (E2), luteinizing hormone (LH), and follicle stimulating hormone (FSH) were measured by enzyme-linked immunosorbent assay using a kit purchased from Dixintai Testing Technology (Beijing) Co., Ltd. All operations were carried out in accordance with the instructions in the kit.

2.4.4 Breast development

Tanner breast staging scale [13] was used to assess the breast development of patients in both groups. This 5-stage scale ranges from 0 to 4 points. 0 points (stage I) marks the breast in the pre-adolescent period. 1 point (stage II) denotes the initial development of nipple and areola, 2 points (stage III) refers to the enlargement, fusion, and protuberance of breast and areola. 3 points (stage IV) represents that nipple and areola protrude above the breast contour. 4 points (stage V) indicates the adult-type breast (i.e., maturity of the breast).

2.4.5 Adverse reaction

The occurrence of adverse reactions such as hyperhidrosis, back pain, dizziness, and dry mouth in both groups was recorded during the treatment.

2.5 Statistical methods

Statistical analysis was performed using SPSS 20.0. Count data were expressed as cases (%), and comparisons between the two groups were carried out using χ^2 test. Continuous variables were analyzed for normality using the Kruskal-Wallis method, and continuous variables that satisfy the normal distribution were expressed as mean ± standard deviation. Independent samples t-test was used for comparison between groups, and paired samples t-test was performed for comparison before and after treatment in the same group. Differences were considered to be statistically significant at two-sided $p < 0.05$.

3 Results

3.1 Comparison of general data between the two groups

The difference of age, BA, height, weight, and Tanner breast staging score in both groups was not statistically significant ($p > 0.05$), but was comparable, as seen in Table 1.

3.2 Comparison of clinical efficacy between the two groups

The total effective rate of clinical efficacy in the dietary group was significantly higher than that in the control group ($p < 0.05$), as seen in Table 2.

3.3 Comparison of BA and bone metabolism between the two groups before and after treatment

Before treatment, there was no statistically significant difference between BA/CA, tPINP, and β-CTX levels in the two groups ($p > 0.05$). After treatment, BA/CA

level in the two groups was reduced ($p < 0.05$), and the level in the dietary group was lower than that in the control group ($p < 0.05$). The tPINP and β-CTX levels in the two groups were elevated ($p < 0.05$), and these levels in the dietary group were higher than those in the control group ($p < 0.05$). The results were displayed in Table 3.

Table 1 Comparison of general data in two group (mean ± standard deviation).

Groups	Cases	Age (years old)	BA (years)	Height (cm)	Weight (kg)	Tanner score (point)
Dietary group	47	8.10 ± 0.54	8.51 ± 0.46	131.41 ± 4.58	28.67 ± 4.52	1.60 ± 0.21
Control group	47	8.14 ± 0.63	8.60 ± 0.51	132.23 ± 4.36	29.12 ± 4.81	1.63 ± 0.18
χ^2/t		0.331	0.898	0.889	0.467	0.744
p		0.742	0.371	0.376	0.641	0.459

Table 2 Comparison of clinical efficacy between the two groups [case (%)].

Groups	Cases	Cured	Significantly effective	Effective	Ineffective	Total effective rate
Dietary group	47	9 (19.15)	16 (34.04)	17 (36.17)	5 (10.64)	42 (89.36)
Control group	47	6 (12.77)	13 (27.66)	15 (31.91)	13 (27.66)	34 (72.34)
χ^2						4.398
p						0.036

Table 3 Comparison of BA and bone metabolism between the two groups before and after treatment.

Groups	Cases	BA/CA		tPINP (ng/mL)		β-CTX (ng/L)	
		Before treatment	After treatment	Before treatment	After treatment	Before treatment	After treatment
Dietary	47	1.06 ± 0.67	0.62 ± 0.34 *	730.54 ± 68.74	846.32 ± 81.13 *	981.52 ± 87.51	1316.62 ± 96.17 *
Control	47	1.09 ± 0.71	0.82 ± 0.50 *	732.66 ± 74.52	792.74 ± 80.21 *	984.33 ± 86.35	1130.55 ± 95.23 *
t		0.211	2.154	0.143	3.220	0.157	9.425
p		0.834	0.034	0.886	0.002	0.876	<0.001

Note: Comparison with before treatment: * $p < 0.05$.

3.4 Comparison of breast development and ovarian function before and after treatment between the two groups

Before treatment, there was no statistically significant difference between the Tanner breast staging score and levels of E2, LH, and FSH levels in the two groups ($p > 0.05$). After treatment, Tanner breast staging score and E2, LH and FSH levels in the two groups were reduced ($p < 0.05$), and these in the dietary group were lower than those in the control group ($p < 0.05$). The results were displayed in Table 4.

3.5 Safety analysis

During the treatment, no adverse reactions such as hyperhidrosis, back pain, dizziness, and dry mouth were found in both groups.

4 Discussion

Idiopathic central precocious puberty is more common in female children and is mainly manifested by the early appearance of adolescent characteristics (such as growth spurts, reproductive organs and sexual characteristics) [14]. In order to find an effective way to treat idiopathic central precocious puberty, this study included 47 children who were treated with dietary intervention combined with Anshen Ziyin Xihuo prescription, and 47 children who were treated only with Anshen Ziyin Xihuo prescription. After

comparison of the clinical efficacy in the two groups, it was found that that dietary intervention combined with Anshen Ziyin Xiehuo prescription has a good clinical efficacy in the treatment of idiopathic central precocious puberty.

Table 4 Comparison of breast development and ovarian function before and after treatment between the two groups.

Groups	Cases	Tanner scale (point)		E2 (pg/mL)	
		Before treatment	After treatment	Before treatment	After treatment
Dietary group	47	1.60 ± 0.21	1.35 ± 0.18 *	30.78 ± 4.23	13.48 ± 2.34 *
Control group	47	1.63 ± 0.18	1.46 ± 0.16 *	30.52 ± 4.61	17.32 ± 2.81 *
t		0.744	3.131	0.285	7.199
p		0.459	0.002	0.776	<0.001
Groups	**Cases**	**LH (IU/L)**		**FSH (IU/L)**	
		Before treatment	**After treatment**	**Before treatment**	**After treatment**
Dietary group	47	0.15 ± 0.04	0.11 ± 0.03 *	14.23 ± 2.62	7.21 ± 1.53 *
Control group	47	0.16 ± 0.05	0.13 ± 0.03 *	14.34 ± 2.47	8.87 ± 1.41 *
t		1.071	3.232	0.209	5.470
p		0.287	0.002	0.835	<0.001

Note: Comparison with before treatment: * $p < 0.05$.

BA/CA is a commonly used indicator for clinical assessment of BA, with higher level indicating a greater difference between BA and CA and a more severe degree of precocious puberty. The tPINP and β-CTX are biomarkers related to bone metabolism, and higher levels of them indicate the more active bone regeneration of patients [15]. The Tanner breast staging scale is used for assessing precocious puberty in girls by second sex characteristics, with higher staging score indicating more rapid breast development and more severe precocious puberty. E2, LH and FSH are common clinical indicators of sex hormones, with higher levels of them suggesting the faster development of ovarian function and the higher degree of precocious puberty in children [16,17]. In this study, dietary intervention combined with Anshen Ziyin Xiehuo prescription slowed the growth of BA and inhibited bone metabolism and development of breast and ovarian in patients with idiopathic central precocious puberty, which had a better efficacy than Anshen Ziyin Xiehuo prescription alone.

In traditional Chinese medicine, the pathogenesis of precocious puberty in girls lies in the imbalance of yin and yang in the kidneys, deficiency of kidney-yin, and exuberance of deficient fire, so its treatment is to nourish yin, tonify the kidneys, and purge fire [18]. In Anshen Ziyin Xiehuo prescription, *Fructus Hordei Germinatus* has the effect of restoring breast milk and eliminating flatulence, *Rehmannia glutinosa*, *Paeoniae Radix Alba* and *Carapax Testudinis* have the effects of nourishing yin and promoting the secretion of saliva or body fluid, *Phellodendron amurense* and *Alismatis Rhizoma* have the effects of removing turbidities, purging the pathogenic fire, and detoxicating, *Anemarrhenae Rhizoma* has the effect of nourishing yin, moistening dryness and clearing away heat and fire. Therefore, the combination of these drugs can achieve the effect of nourishing Yin and purging the pathogenic fire [7]. As modern pharmacological studies shown, *Anshen Ziyin Xiehuo* prescription affects sex hormone levels in patients with precocious puberty, where the total saponins of *Anemarrhenae Rhizoma* in *Anemarrhenae Rhizoma* can affect the sex

hormones of female rats through the hypothalamus-pituitary-gonadal axis, and amine compounds in *Fructus Hordei Germinatus* can inhibit the secretion of prolactin and estrogen [19,20]. Zhu et al. found that sweets, tonic foods, and high-protein foods were all risk factors for central precocious puberty in children [21,22]. Besides, Meng's research also pointed out that excessive intake of high-fat and high-calorie foods may lead to excess calories and convert them into fat, which can raise the body's sex hormone levels and trigger precocious puberty [23]. As the study by Ana et al. demonstrated, children who consumed more fresh vegetables and fruits had a later onset of puberty than those who consumed less [1]. From these findings, it can be seen that dietary intervention can regulate the dietary structure of children, reduce the intake of high-protein, high-fat, and high-calorie foods, and increase the intake of fresh fruits and vegetables, so as to achieve the purpose of ensuring balanced nutrition and avoiding excessive accumulation of calories, thereby regulating the levels of sex hormones in the body and improving precocious puberty [9]. Therefore, dietary intervention combined with Anshen Ziyin Xiehuo prescription was effective in treating children with idiopathic central precocious puberty.

In addition, no adverse reactions such as hyperhidrosis, back pain, and dizziness were found during the treatment in this study. This result suggested that dietary intervention combined with Anshen Ziyin Xiehuo prescription had a better safety and could be promoted in the clinic.

However, due to the limited clinical samples and observation time in this study, there may be certain limitations. In the later stage, it is still necessary to expand the sample size and extend the observation time. Randomized controlled trials are conducted to avoid coincidences, and further research will be performed to fathom out the specific effects of dietary intervention combined with Anshen Ziyin Xiehuo prescription in the treatment of children with idiopathic central precocious puberty.

In conclusion, dietary intervention combined with Anshen Ziyin Xiehuo prescription has good clinical efficacy in the treatment of idiopathic central precocious puberty, which can slow down the growth of BA and inhibit bone metabolism as well as development of breast and ovarian, with good safety.

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Not applicable.

Conflicts of Interest

The authors report there are no competing interests to declare.

Author Contributions

K.C. and H.X. conceptualized the trial, and participated in creating the study design and the statistical analysis plan. X.Q. made the first draft of the manuscript. All authors reviewed and revised the manuscript critically for important intellectual content, reviewed and approved the final manuscript.

Ethics Approval and Consent to Participate

This study was approved by the Ethics Committee of our hospital, and all the enrollees signed the written informed consent.

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Availability of Data and Materials

The data presented in this study are available on request from the corresponding author.

Supplementary Materials

Not applicable.

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