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Study on TCM Syndrome Distribution Characteristics and Hypothalamic-Pituitary-Gonadal Axis-Related Indicators in Girls with Central Precocious Puberty

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Abstract: ***Objective:*** *To explore the distribution characteristics of Traditional Chinese Medicine (TCM) syndromes in girls with central precocious puberty (CPP) and their correlations with indicators related to the hypothalamic-pituitary-gonadal (HPG) axis.* ***Methods:*** *A cross-sectional observational study design was adopted. A total of 122 girls diagnosed with CPP who visited the Department of Pediatric Endocrinology, the Second Affiliated Hospital of Shaanxi University of Chinese Medicine between March 2024 and September 2025 were enrolled. Western medicine diagnosis was implemented in accordance with the Expert Consensus on the Diagnosis and Treatment of Central Precocious Puberty (2022). TCM syndrome differentiation was conducted based on the Clinical Diagnostic and Therapeutic Guidelines of Pediatric TCM: Precocious Puberty combined with clinical expert experience. All patients were categorized into three syndrome types: yin deficiency with effulgent fire, liver depression transforming into fire, and internal accumulation of phlegm-heat. We analyzed the distribution of TCM syndromes and their associations with age at onset, disease course, Tanner breast staging, body mass index (BMI), uterine and ovarian development, and basal sex hormone levels.* ***Results:*** *(1) Among the 122 girls with CPP, 59 cases (48.36%) presented yin deficiency with effulgent fire, 40 cases (32.79%) internal accumulation of phlegm-heat, and 23 cases (18.85%) liver depression transforming into fire. Yin deficiency with effulgent fire was the predominant syndrome type. (2) Statistically significant intergroup differences were observed across syndrome types in age at onset, disease course, BMI stratification, Tanner breast staging, and partial HPG axis-related indicators. Girls with internal accumulation of phlegm-heat had a higher proportion of overweight and obesity as well as relatively longer disease courses; those with yin deficiency with effulgent fire exhibited a younger average age at onset. Basal luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels differed significantly among the three syndrome groups, indicating a correlation between TCM syndrome differentiation and the activation status of the HPG axis. (3) As disease course prolonged, uterine length, uterine volume, and bilateral ovarian volumes all showed an upward trend. Basal LH, FSH and estradiol (E_2) levels also generally increased, demonstrating that disease progression was closely correlated with HPG axis activation and enhanced development of target reproductive organs.* ***Conclusion:*** *The TCM syndrome distribution among girls with CPP is dominated by yin deficiency with effulgent fire, followed by internal accumulation of phlegm-heat, while liver depression transforming into fire accounts for the smallest proportion. Distinct TCM syndrome types differ in disease course, physical development, sexual maturation severity, and HPG axis-related biomarkers, suggesting that TCM syndrome differentiation can partially reflect the clinical heterogeneity of CPP.*

Keywords: Central Precocious Puberty, Yin Deficiency with Effulgent Fire, Internal Accumulation of Phlegm-Heat, Liver Depression Transforming into Fire, Hypothalamic-Pituitary-Gonadal Axis.

1. Introduction

Precocious puberty (PP) is an abnormal disorder of growth and development characterized by premature initiation of puberty and early emergence of secondary sexual characteristics. Per the domestic diagnostic criteria for precocious puberty, a diagnosis is confirmed if girls develop secondary sexual characteristics before 7.5 years old, boys before 9 years old, or girls experience menarche prior to 10 years old [1]. The incidence of precocious puberty is currently on the rise, reaching up to 0.6% among children [2]. Based on etiology and pathogenesis, PP is classified into central precocious puberty (CPP), peripheral precocious puberty, and incomplete precocious puberty. CPP is the most prevalent subtype, predominantly affecting girls, with a female-to-male incidence ratio of approximately 5–10:1 [3].

2. Research Methods

2.1 Research Subjects

Female pediatric patients diagnosed with CPP who attended the Department of Pediatric Endocrinology, the Second Affiliated Hospital of Shaanxi University of Chinese Medicine from March 2024 to September 2025.

2.2 Western Medicine Inclusion Criteria

Western diagnostic standards referenced the *Expert Consensus on the Diagnosis and Treatment of Central Precocious Puberty (2022)* published in 2022 [4]:

1) Premature secondary sexual characteristics: girls develop secondary sexual characteristics before 7.5 years old or menarche before 10 years old;

2) Gonadal enlargement: Pelvic ultrasonography reveals enlarged uterine and ovarian volume with multiple ovarian follicles >4 mm in diameter;

3) Accelerated linear growth: Annual growth velocity exceeds that of normal peers;

4) Advanced bone age: Bone age surpasses chronological age by ≥1 year;

5) Standard GnRH stimulation test: Peak LH >5 U/L, peak LH/FSH ratio >0.6, with serum gonadotropin and sex hormone levels consistent with pubertal status.

2.3 TCM Inclusion Criteria

Referenced the syndrome differentiation criteria for phlegm-damp stagnation in the *Guidelines for Integrated Traditional Chinese and Western Medicine Diagnosis and Treatment of Precocious Puberty in Children (2023 Edition)* [5].

- Primary symptoms: (1) Premature breast development; (2) Increased vaginal discharge.
- Secondary symptoms: (1) Limb heaviness; (2) Sticky mouth; (3) Chest distress and frequent sighing; (4) Loose stools; (5) Thick and greasy tongue coating. Diagnosis is confirmed when all primary symptoms plus any three secondary symptoms are present.

2.4 Exclusion Criteria

(1) CPP induced by organic lesions of the central nervous system, confirmed via hypothalamic-pituitary MRI;

(2) Precocious puberty caused by gonadal tumors, adrenal disorders, or exogenous intake of sex hormone-containing drugs/foods;

(3) CPP transformed from peripheral precocious puberty;

(4) Precocious puberty secondary to other endocrine disorders (e.g., McCune-Albright syndrome);

(5) Poor treatment compliance or treatment interruption;

(6) Incomplete laboratory test data.

2.5 Clinical Data Collection

Specialist pediatric endocrinologists performed physical examinations on all subjects, including height and weight measurement for BMI calculation, evaluation of secondary sexual characteristics and Tanner staging. Auxiliary examinations including serum sex hormone assays (LH, FSH, E_2), pelvic ultrasound of uterus and ovaries, and bone age assessment were completed for all patients.

2.6 Statistical Analysis

Statistical analyses were performed using SPSS 26.0 software. A P-value <0.05 was defined as statistically significant.

- Normally distributed measurement data were expressed as mean ± standard deviation (x±s); independent samples t-test was used for two-group comparisons, one-way analysis of variance (ANOVA) for multi-group comparisons, with LSD or Bonferroni methods for post-hoc pairwise comparisons.
- Non-normally distributed measurement data were presented as median (25th percentile, 75th percentile) [M (P25, P75)]; Mann–Whitney U test for two-group comparisons, Kruskal–Wallis H test for multi-group comparisons.
- Enumeration data were recorded as case number and constituent ratio [n (%)]; intergroup comparisons were conducted via Pearson Chi-square test.

2.7 Ethical Approval

This clinical trial was approved by the hospital Ethics Committee prior to implementation.

2.8 Subject Recruitment and Informed Consent

Prior to study enrollment, written informed consent was obtained from the legal guardians of all child subjects by pediatric endocrinologists.

3. Results

3.1 General Clinical Characteristics of Girls with CPP

A total of 122 eligible girls with CPP were included. Their chronological age ranged from 4 to 10 years, with a mean age of 7.57±0.94 years and a median age of 8.00 (7.00, 8.00) years. The results indicated that the age of onset of CPP in the enrolled patients was predominantly between 7 and 8 years, with 8 years as the most common age.

Table 1: Age Distribution of Girls with CPP (n=122)

Age (years)	Cases (n)	Constituent ratio (%)
4	1	0.82
5	3	2.46
6	10	8.20
7	30	24.59
8	71	58.20
9	4	3.28
10	3	2.46

3.2 Constituent Ratios of the Three TCM Syndrome Types in Girls with CPP

Yin deficiency with effulgent fire was the most prevalent syndrome (59 cases, 48.36%), followed by internal accumulation of phlegm-heat (40 cases, 32.79%), and liver depression transforming into fire (23 cases, 18.85%). The intergroup distribution of the three syndromes showed statistically significant differences (P<0.05). This finding suggested that yin deficiency with effulgent fire constitutes one of the core pathogeneses of CPP in girls.

Table 2: Distribution of TCM Syndromes (n=122)

TCM Syndrome Type	Cases (n)	Constituent ratio (%)	TCM Syndrome Type
Yin deficiency with effulgent fire	59	48.36	Yin deficiency with effulgent fire
Internal accumulation of phlegm-heat	40	32.79	Internal accumulation of phlegm-heat
Liver depression transforming into fire	23	18.85	Liver depression transforming into fire

3.3 Comparison of BMI Indicators Across Different TCM Syndrome Types

Statistically significant differences were observed in BMI

stratification distribution among the three syndrome groups. Post-hoc pairwise comparisons revealed significant differences in BMI distribution between internal accumulation of phlegm-heat and yin deficiency with effulgent fire, as well as between internal accumulation of phlegm-heat and liver depression transforming into fire (all $P<0.05$). No significant difference was detected between yin deficiency with effulgent fire and liver depression transforming into fire ($P>0.05$). Obesity showed a highly specific correlation with internal accumulation of phlegm-heat, while normal or lean body habitus was more frequently observed in yin deficiency with effulgent fire and liver depression transforming into fire.

Table 3: Comparison of BMI Stratification Distribution Among Different TCM Syndrome Groups

TCM Syndrome Type	Normal/Lean [n (%)]	Overweight/Obese [n (%)]	Primary Feature
Yin deficiency with effulgent fire	40 (67.8)	19 (32.2)	Predominantly normal/lean
Internal accumulation of phlegm-heat	8 (20)	32 (80)	Predominantly obese
Liver depression transforming into fire	15 (65.2)	8 (34.8)	Predominantly normal/lean

3.4 Serum Basal Sex Hormone Levels Across TCM Syndrome Types

Basal serum sex hormone levels differed significantly among the three syndrome groups. Overall comparisons of basal LH, FSH and E_2 levels yielded statistically significant differences ($P<0.05$). Further pairwise comparisons showed significant differences between internal accumulation of phlegm-heat and yin deficiency with effulgent fire, as well as between internal accumulation of phlegm-heat and liver depression transforming into fire, while no statistical difference existed between liver depression transforming into fire and yin deficiency with effulgent fire. In general, patients with internal accumulation of phlegm-heat exhibited higher basal LH, FSH and E_2 concentrations, whereas levels were relatively lower in the yin deficiency with effulgent fire and liver depression transforming into fire groups, implying divergent degrees of HPG axis activation across TCM syndromes.

Table 4: Comparison of Sex Hormone Indicators Among Different TCM Syndrome Groups

TCM Syndrome Type	LH (mIU/ml)	FSH (mIU/ml)	E_2 (pg/ml)
Yin deficiency with effulgent fire	1.85±0.90	2.28±0.35	35.66±0.19
Internal accumulation of phlegm-heat	3.33±0.86	2.64±0.41	45.15±0.32
Liver depression transforming into fire	2.20±0.73	2.57±0.36	37.82±0.20

3.5 Syndrome-Specific Degree of Advanced Bone Age

- The median bone age advancement of patients with yin deficiency with effulgent fire was 1.16 (0.63, 1.69) years, representing the mildest bone maturation acceleration with high inter-individual variability;
- Mean bone age advancement of liver depression transforming into fire patients was 1.22±0.74 years (moderate advancement);
- Patients with internal accumulation of phlegm-heat demonstrated the most prominent bone age advancement, with a mean value of 1.46±0.63 years, significantly higher than the other two groups.

These preliminary results indicated that internal accumulation of phlegm-heat is associated with more pronounced acceleration of skeletal maturation.

Table 5: Comparison of Bone Age Advancement Among Different TCM Syndrome Groups

TCM Syndrome Type	Statistical Index	Bone Age Advancement (years)	Severity of Advancement
Yin deficiency with effulgent fire	Median (P25, P75)	1.16 (0.63, 1.69)	Mildest
Internal accumulation of phlegm-heat	Mean ± SD	1.46±0.63	Most severe
Liver depression transforming into fire	Mean ± SD	1.22±0.74	Moderate

3.6 Uterine and Ovarian Developmental Characteristics of Different TCM Syndromes

Significant intergroup differences were found in uterine developmental parameters. Post-hoc pairwise comparisons demonstrated that uterine length and uterine volume were markedly lower in the yin deficiency with effulgent fire group relative to the internal accumulation of phlegm-heat group, indicating more advanced uterine maturation in patients with internal accumulation of phlegm-heat, possibly linked to their distinct metabolic and endocrine milieu.

In terms of ovarian development, bilateral ovarian volumes were larger in the internal accumulation of phlegm-heat group than in the yin deficiency with effulgent fire group. Increased ovarian volume directly reflects enhanced follicle recruitment and activation, suggesting earlier or more robust HPG axis initiation in patients with internal accumulation of phlegm-heat.

Table 6: Comparison of Uterine and Ovarian Developmental Indicators Among Different TCM Syndrome Groups

TCM Syndrome Type	Uterine Length (cm)	Uterine Volume (ml)	Left Ovarian Volume (ml)	Right Ovarian Volume (ml)
Yin deficiency with effulgent fire	3.43±0.10	2.53±0.31	1.80±0.29	1.62±0.25
Internal accumulation of phlegm-heat	4.82±0.36	3.89±0.40	4.00±0.42	3.62±0.46
Liver depression transforming into fire	3.45±0.16	2.75±0.34	2.65±0.30	2.06±0.26

4. Discussion

4.1 Distribution Pattern of TCM Syndromes in Girls with CPP and Its Modern Medical Implications

This study identified a regular distribution of TCM syndromes among girls with CPP, prioritized by yin deficiency with effulgent fire, followed by internal accumulation of phlegm-heat and liver depression transforming into fire. This distribution aligns with existing literature stating that yin deficiency with effulgent fire is the most dominant syndrome [6-10]. It is implied that CPP arises from complex

pathogeneses rooted in kidney yin insufficiency, complicated by secondary pathological factors including phlegm-damp and stagnant fire. The high proportion of yin deficiency with effulgent fire demonstrates that internal yin depletion and hyperactive ministerial fire constitute a core pathological basis for CPP, consistent with the physiological characteristics of children described as "intrinsic yin insufficiency and relative yang excess" in TCM theory [11,12]. The substantial proportion of internal accumulation of phlegm-heat highlights the pathogenic roles of obesity and metabolic disturbance in CPP progression; though less prevalent, liver depression transforming into fire reflects the involvement of emotional factors in disease onset.

From a modern endocrinological perspective, the core pathogenesis of CPP lies in premature activation of the HPG axis, with obesity, insulin resistance and dysregulated adipokines established as critical predisposing factors [13-15]. The prominent proportion of internal accumulation of phlegm-heat in this cohort aligns with contemporary research confirming a tight correlation between obesity and CPP, implying a potential correspondence between the TCM pathological state of "phlegm-damp retention" and modern metabolic dysfunction. Divergent sexual developmental markers across syndrome types further support that TCM syndrome differentiation partially mirrors the clinical heterogeneity of CPP. The layered distribution of TCM syndromes in CPP patients, with yin deficiency with effulgent fire as the primary pattern and phlegm-heat retention and liver fire stagnation as concurrent compound pathogeneses, provides clinical evidence for understanding CPP under the integrated "disease-syndrome" framework and lays a foundation for subtype-specific intervention and individualized treatment.

4.2 Correlation Between Internal Accumulation of Phlegm-Heat and Obesity in CPP Pathogenesis

A high proportion of patients with internal accumulation of phlegm-heat presented elevated BMI, revealing a close association between this syndrome, obesity and metabolic dysfunction. TCM theory attributes phlegm-damp formation to impaired spleen transportation and retention of water-dampness [16]; modern medicine regards obesity as a manifestation of energy metabolism disorder and a major risk factor for precocious puberty onset [17]. The two theoretical systems share overlapping pathological foundations. Previous studies have confirmed that adipose tissue secretes leptin, adiponectin and other bioactive factors, which modulate HPG axis function via insulin, IGF-1 and downstream signaling pathways to advance pubertal initiation [18]. In this study, patients with internal accumulation of phlegm-heat exhibited high overweight/obesity rates and markedly advanced bone age, suggesting this syndrome corresponds to a CPP subtype dominated by obesity and metabolic dysregulation. In other words, the TCM diagnosis of internal accumulation of phlegm-heat not only represents a syndrome classification, but also reflects prominent systemic metabolic imbalance. Clinically, for patients presenting this syndrome, management should extend beyond monitoring sexual maturation progression to include weight control, dietary and exercise guidance, and systematic metabolic assessment. TCM therapeutic strategies focusing on invigorating the spleen, resolving phlegm, dispelling dampness and descending turbidity offer auxiliary benefits for restoring systemic internal homeostasis.

4.3 Correlation Between TCM Syndromes and the Degree of HPG Axis Activation

Significant intergroup differences in uterine-ovarian developmental parameters and basal sex hormone levels across TCM syndromes indicate a potential correlation between syndrome types and the magnitude of HPG axis activation. Patients with internal accumulation of phlegm-heat exhibited more pronounced sexual developmental markers, suggesting this syndrome correlates with stronger or longer-duration HPG axis activation. From TCM perspective, each syndrome encapsulates the holistic pathological state of the body at a specific disease stage; modern endocrinology defines CPP as premature initiation of the neuroendocrine regulatory network [19]. Divergent clinical indicators across syndromes reflect heterogeneous metabolic statuses, endocrine profiles and developmental trajectories. Notably, internal accumulation of phlegm-heat frequently coexists with elevated BMI, and obesity itself amplifies HPG axis activation through multiple metabolic and endocrine pathways, rendering this syndrome representative of CPP driven predominantly by metabolic factors. By contrast, yin deficiency with effulgent fire and liver depression transforming into fire present distinct features in age at onset, disease course and sexual developmental markers, implying they predominantly reflect functional internal imbalance, emotional disturbance or excessive internal heat [20]. Although this cross-sectional study cannot establish causal relationships between TCM syndromes and HPG axis activation intensity, the consistent correlations between syndrome classification, hormone levels and reproductive developmental biomarkers demonstrate that TCM syndrome differentiation is not purely subjective, but bears tangible biological underpinnings. This study supports interpreting CPP heterogeneity via the "syndrome-clinical phenotype" paradigm. Further research incorporating GnRH stimulation test results, comprehensive metabolic biomarkers and multimodal imaging data is required to fully elucidate the biological signatures corresponding to distinct TCM syndromes.

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