Precocious Puberty in Boys: A Study Based on 5 Years of Data From a Single Center in Northern China

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Abstract
Aims: To evaluate the clinical features and etiology of precocious puberty in Chinese boys.
Methods: In this study, data from boys who were referred for the evaluation of precocious puberty from 2015 to 2020 at a tertiary hospital in Northern China were retrospectively analyzed.
Results: Eighty-two boys were diagnosed with precocious puberty (PP) from 2015 to 2020. Sixty-two patients (75.6%) were diagnosed with central precocious puberty (CPP), and twenty patients (24.4%) were diagnosed with peripheral PP (PPP). In the CPP group, forty-nine cases were classified as idiopathic CPP (ICPP), and thirteen patients had pathogenic CPP. The top three causes of PPP were congenital adrenal hyperplasia (CAH), germ cell tumors (GCTs) secreting human chorionic gonadotropin (hCG), and familial male-limited precocious puberty (FMPP).
Conclusions: The etiology of precocious puberty in males is diverse. The majority of CPP cases in Chinese boys are idiopathic rather than organic.
Keywords: Male, Precocious puberty, Etiology

Introduction
Precocious puberty (PP) in boys refers to the development of secondary sexual characteristics before 9 years of age. The prevalence of PP is approximately 10 times lower in boys than in girls (1). Female PP is mostly idiopathic, while male PP may be due to pathological factors. However, there are fewer studies on male than female PP, and the male studies included fewer patients. The proportion of organic CPP in males is 26%~64% (2-4). Over 15 years in South Korea, Jisun Lee et al. reported that 38% (27/71) of cases of male PP were organic CPP, and the majority were due to intracranial diseases or tumors (3). Lisa Swartz Topor et al. reported all cases of male CPP seen at a US pediatric hospital for 10 years; almost two-thirds of the boys were overweight/obese, and more than 60% had neurogenic CPP (4). Neurofibromatosis type I (NF1) was the most common diagnosis. In one Polish
study, 16 boys were referred for evaluation in the hospital because of pubertal signs; 50% were diagnosed with precocious adrenarche, 4 with central nervous system tumors, 2 with CAH, 1 with a Leydig cell tumor and 1 with idiopathic CPP (5).

Few studies have analyzed peripheral PP (PPP) and CPP together, and most studies have focus solely on either male CPP or male PPP. We did not focus exclusively on CPP or PPP because central and peripheral manifestations sometimes overlap. In fact, males with PPP can present with CPP because of complexity. Studies from different countries and regions seem to support the role of pathological factors in males with PP, but the etiology is not the same. Data on male PP are still insufficient. Therefore, we conducted this retrospective study on male PP diagnosed at tertiary hospitals in northern China, and we analyzed the clinical manifestations and etiology.

Materials and Methods

Subjects and Clinical Assessment

This retrospective study included patients who were evaluated for PP between 2015 and 2020 at the Department of Endocrinology, Children's Hospital Capital Institute of Pediatrics, Beijing, China. PP was defined as the onset of secondary sexual characteristics before 9 years of age, and the medical records of each patient were complete (6). Patients who had previously been diagnosed at other hospitals and those with variants of precocious puberty (premature adrenarche, PA) were excluded from the analysis.

The clinical, laboratory, radiological, and molecular study data (if needed) were evaluated for all patients. Chinese growth charts for children were applied to interpret growth data, which were described as standard deviation score (SDS) values (7). The diagnosis of CPP was made based on a clinical evaluation, which included taking a detailed history of the patient and his caregivers, followed by a physical examination and Tanner staging. Testicular volume was assessed using an orchidometer. All boys included in this study underwent blood collection for the measurement of luteinizing hormone (LH), follicle-stimulating hormone (FSH), testosterone (T). Bone age was assessed by a single pediatric endocrinologist and a radiologist using the comparative method of Greulich and Pyle method. Cranial/pituitary MRI was mandatory in all cases, and cerebrospinal fluid (CSF) sampling was required when a GCT was strongly suspected. A diagnosis of CPP was confirmed via elevated LH response in a GnRH (Gonadotropin-releasing hormone) analog stimulation test (subcutaneous triptorelin: Ferring, Hoechst, Frankfurt, Germany, 0.1 mg/m², to a maximum of 0.1 mg). CPP was defined as peak LH >7 IU/L and bone age 1 year greater than chronological age (8).

Congenital adrenal hyperplasia (CAH) was diagnosed based on elevated 17-OHP, progesterone and ACTH; decreased cortisol, with or without hyperkalemia and hyponatremia; and a CT or ultrasound scan suggesting adrenal hyperplasia (9). Patients with central nervous system (CNS) GCTs were diagnosed through histopathology and/or elevated CSF hCG levels (normal: <0.1 IU/L) and the appearance of an intracranial mass on MRI (10). Patients with hypothalamic hamartomas (HHs) were diagnosed with CPP, either isolated or in combination with seizures, and their MRI scans showed a mass either located adjacent to hypothalamic structures (i.e., in a parahypothalamic position) or infiltrating the hypothalamus (11). Familial male-limited precocious puberty (FMPP) was diagnosed in boys who had a family history of PP, normal hCG levels and a constitutively activated mutant luteinizing hormone receptor (LHCGR) leading to elevated testosterone synthesis (12). Leydig cell tumors, optic pathway tumors and choriocarcinomas were diagnosed using histopathological proof. The study protocol was approved by the Children's Hospital Capital Institute of Pediatrics Ethics Committee (SHERLL2020003). We divided the boys into two groups: the CPP (gonadotropin-dependent) group and the PPP (gonadotropin-independent) group.

Molecular analysis

Genomic analysis of LHCGR was performed by direct sequencing. Genomic DNA was extracted from peripheral blood lymphocytes. The coding regions and intron–exon boundaries of LHCGR were amplified by polymerase
chain reaction (PCR). The pathogenicity of each variant was interpreted according to American College of Medical Genetics and Genomics (ACMG) standards and categorized (13).

Statistical Analysis
Statistical analyses were conducted using SPSS version 22.0. The normality of the distribution was confirmed, the results were expressed as the mean ± SD, and t-tests for independent samples were applied. P-values below 0.05 were regarded as statistically significant.

Results
Eighty-seven boys were admitted to our hospital for the evaluation of pubertal development. After clinical and laboratory evaluation of all patients except those with PA (5 boys), a total of 82 boys were diagnosed with PP. The patients’ age at the time of referral ranged from 0.92 to 10.5 years; 73.5% were over 7 years old at the time of their first visit, 20.7% were 3 to 6 years old, and 7% were under 3 years old (Figure 1). The main complaints included penis and/or testis enlargement (45, 54.8%), growth acceleration (45, 54.8%), the development of pubic and/or axillary hair (39, 47.6%), voice change (10, 12.2%), breast mass (5, 6.1%), acne (4, 4.9%), and erection/ejaculation (2, 2.4%).

Sixty-two boys (75.6%) were diagnosed with CPP, and 20 boys were diagnosed with PPP (24.4%). The average evaluation age of the PPP group was much lower than that of the CPP group (5.50±2.23 years vs 8.83±2.19 years, p<0.001), while the testosterone levels did not differ significantly (10.06±7.14 nmol/L vs 12.71±12.84 nmol/L, p=0.270). The difference in bone age and chronological age in PPP patients was significantly higher than that in CPP patients (4.44±2.41 years vs 2.26±1.31 years, p=0.001). Descriptive data are listed in Table 1 and Table 2.

In the CPP group, 49 boys were diagnosed with idiopathic CPP (ICPP, 79%). Thirteen boys were diagnosed with pathogenic CPP (21%), including all cases of HH and PBMT, 3 cases of CAH, 1 case of optic pathway tumor and 1 undetermined case (Figure 2).

HH
Five patients were diagnosed with HH (0.92–8.17 years). The imaging findings were assessed by two radiologists (Figure 3A). The patients’ basal LH levels (7.70±8.35) were consistent with the diagnosis of CPP. Four cases were of the “parahypothalamic type”, in which the hamartoma is attached only to the floor of the third ventricle or tethered to the floor by a peduncle, and two of the patients presented gelastic seizures. One case was of the “intrahypothalamic type”, in which the hamartoma is involved or enveloped by the hypothalamus and the tumor distorts the third ventricle; this patient presented gelastic seizures as well.

PBMT
Three patients (1 with Fanconi anemia, 1 with myelodysplastic syndrome and 1 with aplastic anemia) received chemotherapy and bone marrow transplantation. Busulfan/cyclophosphamide (BU/CY) was used as the conditioning regimen for myelodysplastic syndrome and aplastic anemia. The patient with aplastic anemia took Epimedium for at least 6–7 months after transplantation. The patient with Fanconi anemia had a conditioning regimen including BU/fludarabine + antithymocyte globulin + TBI. PP occurred 1–3 years after allogeneic hematopoietic stem cell transplantation. All 3 patients presented CPP.

The etiology of CPP in one 3-year-old boy remains unknown. He had enlarged testes shortly after birth, and he was admitted to our department because of extremely large, symmetrical testes (25 mL). His test results showed an LH peak of 4.17 IU/L, an FSH peak of 28.3 IU/L and extremely high testosterone (17.15 nmol/L). He had a long face, large ears, white skin color and mild mental retardation. A testicular biopsy sample revealed normal findings. The MRI findings and hCG and 17-OHP results were normal. The results of a fragile X test were negative.

Whole-exome sequencing or microarray examination showed no typical mutations in the genes KISS1, KISS1R, MKRN3 or DLK1.

In the PPP group, CAH (9 cases), central nervous system GCT (6 germinomas, 1 choriocarcinoma) and FMPP (3
cases) were the most common causes (45%, 35% and 15%, respectively). We also diagnosed a boy with a Leydig cell tumor (5%) (Figure 2).

**Tumor causes**

In all, 9 boys had tumors (2.25 to 10.0 years), including 7 boys with CNS GCTs, 1 boy with a Leydig cell tumor (chief complaint: testis mass on the left side; laboratory examinations consistent with PPP) and 1 boy with an OPT (chief complaints: blurred vision and growth acceleration; laboratory examinations consistent with CPP), all of which were diagnosed by histopathology. Among patients with GCTs (Figure 3B), 6 showed moderately elevated hCG in serum (0.1~40.6 IU/L) and/or CSF (20.5~32.3 IU/L); their tumor sites were suprasellar (n=3) or in the basal ganglia (n=3). One 2.5-year-old boy presented rapid pubertal development; testing showed remarkably elevated hCG (10000 IU/L). hCG in patients with GCTs was significantly elevated, and the other patients had hCG levels that were below the lower limit of detection. MRI of one boy revealed an approximately 5.6×6.7×12.8 mm mass in the pineal gland (Figure 3C), and biopsy showed choriocarcinoma. Computed tomography scans of the abdomen, pelvis and chest were normal in all of the GCT patients. In the 7 GCT patients, although their testicular volumes varied from 4 mL to 8 mL, all of the GnRHa stimulation tests revealed a prepubertal response to gonadotropin (LH peak: 0.42±0.39).

**FMPP (OMIM #176410)**

LHCGRC gene screening was performed in 3 unrelated boys (patients coded A, B and C) (1.67 to 4.41 years old) (Figure 4). In patients A and B, sequencing analysis of the LHCGRC gene revealed a heterozygous C-to-T transition at codon 577 (c.1730C>T), and this transition led to the substitution of threonine with isoleucine at codon 577 (p.T577I). The two patients’ mothers were heterozygous for the p.T577I mutation, while neither patient’s father carried the mutation. Patient C had a heterozygous T-to-C transition at codon 576 (c.1726T>C) of the LHCGRC gene, and this transition led to the substitution of phenylalanine with leucine at codon 576 (p.F576L). Patient C’s father (who was also a patient) was heterozygous for the p.F576L mutation, while the mother did not carry the mutation.

**CAH (PPP combined with CPP)**

All 12 boys (3.25 to 7.67 years) were diagnosed with a 21-hydroxylase deficiency. Twelve boys presented with penis enlargement, and 3 presented with premature pubarche. Nine boys presented with PPP, and 3 patients presented with CPP. The evaluation age of the CAH-PPP group was slightly lower than that of the CAH-CPP group (5.03±1.42 vs 6.00±1.86 years, p=0.360), and the 17-OHP levels were slightly higher (76.49±78.30 vs 39.80±18.11, p=0.222) but showed no significant difference. In the CAH-CPP group, 1 patient presented CPP before the administration of hydrocortisone, and the other 2 patients presented CPP 6 months and 1 year after treatment. The testicular volumes of the latter two were both 2 mL before treatment but increased to 4 mL and 5 mL, respectively, after treatment. The basal value of LH increased from 0.1 to 0.4 and 5 IU/L, respectively.

**Discussion**

Of the 62 boys who were diagnosed with CPP in our department, 79% were diagnosed with ICPP. No pathological factors were found during the follow-up. Such a high proportion of ICPP is quite different from what has been reported in other countries. Studies have shown that 50~70% of boys with CPP have identifiable pathological changes (6). The majority (64%) of boys with CPP in a ten-year study in Boston had organic CPP (4). A study from Saudi Arabia reported that organic CPP accounted for 50% of CPP cases in boys (14). This discrepancy may be caused by several factors. Previous studies have suggested that there is a downward trend in the age of puberty onset in boys (15,16). The same trend may have occurred in our patients. Increased awareness may be another cause of the increased number of ICPP diagnoses. At the same time, genetic background could play a role, as suggested by the difference in neurofibromatosis rates: neurofibromatosis was the main cause of CPP in the Boston
study but was not found in a single case in our study.

Other than ICPP, HH was the most common etiology of CPP in our study. Lesions or malformations of the CNS are usually considered first in the differential diagnosis of organic CPP. The main risk factors for a physical CNS etiology include young age and male sex (17,18). The most common CNS lesion associated with pathogenic CPP is HH, which is a rare congenital nonneoplastic central nervous system lesion containing mature tissue in a heterotopic location (19). For most symptomatic patients with HH associated with CPP and/or gelastic seizures, the relationship between the neuroradiological findings and clinical presentation has not been fully investigated (20,21). In our study, 41.6% of patients with pathogenic CPP had HHs. However, in the US, 64% of boys with CNS-CPP had neurofibromatosis type I (4). This suggests that the etiology of CPP differs among different races. We also found that in addition to the usual etiology, a relatively rare but not negligible cause of male CPP is prior BMT. Most studies suggest that gonadal impairment is an important side effect in transplanted patients, and busulfan conditioning regimens and TBI are associated with gonad damage (22,23). Interestingly, three patients developed CPP after bone marrow transplant. A Korean study suggested that the application of cyclophosphamide may be related to PP (3). In our study, only 2 patients’ conditioning regimens included cyclophosphamide. One of our patients had a long history of using Epimedium, which has the effect of enhancing sexual function in mice (24).

In addition to chemotherapy and herbal remedies, cranial irradiation might cause damage to gamma-aminobutyric acid–secreting neurons, which could lead to premature activation of GnRH neurons (25). Further studies are needed to determine whether bone marrow transplantation and irradiation could be associated with male CPP.

The spectrum of male PPP is complex. In our study, CAH, GCT and FMPP were the three most common etiologies of PPP. CAH is the predominant etiology in boys with PPP (26). In a six-year retrospective study of PP cases at a tertiary hospital in Southern China, 38% were due to CAH (27). CAH was also the most common etiology of organic PP in our study, occurring in 12 patients. Three patients with CAH developed CPP. Secondary CPP may complicate CAH. First of all, chronic hyperandrogenemia may trigger the activation of the hypothalamic-pituitary axis, leading to CPP (28,29). And hydrocortisone treatment reduces androgen levels and activates gonadotropins. The decrease in sex steroids during treatment of the primary underlying disorder causes activation of the precociously matured hypothalamic GnRH pulse generator via feedback mechanisms, resulting in secondary CPP (30). CPP can occur either before or after treatment. This combination of PPP and CPP in patients with CAH is worthy of our attention, and better clinical management of patients is needed.

Usually, patients with hCG-secreting GCTs present signs of increased intracranial pressure and diabetes insipidus, and PPP is less common than other manifestations (31). In a study by Zeynep Atay et al. that excluded CAH, hCG-secreting tumors, Leydig cell tumors and adrenocortical tumors played equally important roles in the etiology of PPP (32). All of our patients had a significant increase in blood and/or CSF hCG. hCG-secreting GCTs can cause PP in boys by stimulating Leydig cells to secrete testosterone, consistent with previous studies almost exclusively in boys (33). Although 7 of our patients had PPP, it has been reported that some boys with hCG-secreting GCTs near the hypothalamus may actually develop CPP (34).

FMPP is an autosomal-dominant form of PPP in males. FMPP is a very rare disorder, affecting approximately 9 individuals per million (35). The LHR gene, located on human chromosome 2p21, encodes a transmembrane receptor expressed on the cell membranes of testicular Leydig cells (36). Affected males usually begin pubertal development by 1–4 years of age, with rapid growth and progressive virilization, and the same characteristics were observed in the present study (37). The most common mutation reported in the literature in the LHCGR gene is a D578G missense mutation (38). In our study, PCR product sequencing revealed a heterozygous adenosine-guanine transition at nucleotide 1730 in codon 577 in 2 boys; this mutation in LHCGR has been identified before (39). One patient was found to have a heterozygous mutation in LHCGR, causing an F576L substitution within TM6 of LHCGR; although this mutation has not been previously reported, given that it occurs in a mutation hotspot in a
patient with a family history, we suspect that it is also pathogenic. All 3 boys presented with PPP, but as seen with CAH, if the diagnosis was delayed, CPP could also be present at the first visit.

Different studies have shown different disease spectra. Based on these five years of data and a review of the literature, we propose a diagnostic algorithm (summarized in Figure 5) (32). Zou et al. reported that 23% of boys with PPP in Southern China had a history of exogenous hormone intake, such as contraceptives, whereas not a single case due to exogenous hormone intake was found among our patients (27). Testicular tumors were also common in the study by Zou et al. (19%) but very rare in our study. Genetic and dietary differences may be among the reasons for these discrepancies. We did not find any cases of McCune-Albright syndrome or hypothyroidism, which have been reported in other studies (40). In addition to untreated primary hypothyroidism, very rare syndromes, such as Prader-Willi syndrome and Sotos syndrome, can also result in PP (41). In addition, some etiologies remain undetermined despite complex examinations.

Study limitations
This study had several limitations. The enrollees were treated at a single medical center, and the data on male PP could vary at other centers. In the ICPP group, further studies are needed to examine the possible contribution of genetic factors. Sequencing and genetic studies are undertaken increasingly often in affected individuals, thereby resulting in a declining number of “idiopathic” cases.

Conclusion
In conclusion, the etiology of PP in boys is diverse. In Chinese males, CPP is mainly idiopathic, and HH is the most common etiology of pathogenic CPP. CAH and GCTs accounted for the etiologies of 80% of PPP cases. PPP patients may become CPP patients, and the diagnosis of some cases remains challenging.

Disclosure Statement
The authors have no conflicts of interest to declare.

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References


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<td>Age at evaluation (years)</td>
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<td>5.5±2.23</td>
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<td>Testis volume(ml)</td>
<td>10.6±5.30</td>
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Tab 1: Comparison between group 1 and group 2.

BMI, body mass index; BLH, basal luteinizing hormone; PLH, peak luteinizing hormone; BFSH, basal follicle stimulating hormone; T, testosterone; BA-CA, bone age-bone age-chronological age.
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<td><strong>Weight Z score</strong></td>
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Tab 2: Comparison between different subgroups of pathogenic PP.

Figure 1.
Figure 4.
Figure 5.
Diagnostic algorithm in boys with precocious puberty

Testes > 4 ml
- GnRHa test
  - LH > 5-7 IU/L
    - CPP
    - Pituitary and/or cranial MRI
      - CNS lesion
      - No CNS lesion
    - Tumor/HH
  - ICPP
- GCT

Testes < 4 ml
- PPP?
  - Androgen exposure?
    - Yes
      - Exogenous
        - 17-OHP, AD
    - No
      - FMPP?
        - Elevated
          - Adrenal ultrasound, genetic screening if necessary
        - Normal
          - Very young age/family history of CPP/Suspected clinical syndrome: genetic test
          - CAAH