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The incidence of brain lesions in central precocious puberty: The main cause for Chinese boys was idiopathic

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Abstract

Objective: Many studies show that brain lesions are the main cause of central precocious puberty (CPP) in males. However, the association rate has not been reported in China. This study aimed to assess the frequency of both abnormal and likely pathologic brain lesions by magnetic resonance imaging (MRI) in Chinese boys with CPP.

Design: This is a retrospective cross-sectional single-centre study.

Patients: 396 CPP boys were recruited from 2011 to 2019 in Children's Hospital, Zhejiang University School of Medicine, and 129 were eligible for our study.

Measurements: Diagnosis age, bone age, weight (kg), height (cm), puberty stage, MRI results and levels of sexual hormone were analysed.

Results: The number of CPP boys is increasing from 2011 to 2019 in China. Brain MRI findings were normal in 83.7% of CPP boys. Only 21 (16.3%) CPP boys were found with abnormal MRI findings including hamartoma, pineal cyst and other minor changes.

Conclusion: In China, there is an increasing trend of male CPP over the last decade and the main cause is idiopathic, rather than pathogenic brain lesions. Further investigations about the aetiology for CPP with pathological brain lesions are needed.

KEYWORDS
brain lesions, central precocious puberty, Chinese boys, prevalence

1 | INTRODUCTION

Precocious puberty (PP) is defined as onset of secondary sexual characteristics before the age of 9 years in boys and 8 years in girls.[1] It is either due to the premature activation of hypothalamic-pituitary-gonadal axis which is defined as central precocious puberty (CPP), or it may be gonadotropin independent.[2] Well-recognized etiological factors for CPP are congenital or acquired brain disorders, genetic and environmental factors, and international adoption.[3,4] A large proportion of the CPP girls are idiopathic (85%–90%), whereas the boys have much higher chance of underlying pathology in central nervous system (CNS).[5] Previous studies showed a diverse prevalence of pathological brain lesions in CPP boys, varying from 25% to 94%.[4,6–10] Thus, it has long been stated that brain lesions must

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be ruled out by magnetic resonance imaging (MRI) in all boys with CPP.[11] Also, insufficient data on brain lesions have been reported in Chinese boys with CPP.

In this study, we aim to evaluate the frequency of both abnormal and likely pathological brain lesions over the past decade and to clarify whether lesions are common cause of CPP in Chinese boys.

2 | MATERIALS AND METHODS

2.1 | Ethical approval

This study was approved by the Medical Ethics Committee of the Children's Hospital, Zhejiang University School of Medicine (2020-IRB-170).

2.2 | Study participants

Chinese boys with the clinical signs of precocious puberty were admitted from 2011 to 2019 at the Department of Endocrinology, Children's Hospital, Zhejiang University School of Medicine. All the participants were carefully followed by practice guideline. The inclusion criteria were the diagnosis of CPP and completion of cranial MRI. Patients with previously known CNS lesions and with precocious puberty attributed by congenital adrenal hyperplasia, epididymal cyst or other postoperative tumours were excluded from the study by design. Inclusion of the male CPP cohort is shown in Figure 1. 129 boys included in the present study were in good health without neurological signs or symptoms, and none of them was internationally adopted or receiving any therapy.

2.3 | Clinical assessments

Onset and progression of pubertal signs, growth velocity, other symptoms, birth history, previous illness and family history were all recorded and assessed by paediatric endocrinologists. Testicular volume was evaluated by palpation using Prader's orchidometer. Pubertal status was staged according to the Tanner stages. Tanner stage 1 was considered pre-pubertal stage whereas Tanner stages 2–5 were considered as pubertal stages. Standing height and weight were measured with a precision of 0.1 cm and 0.1 kg, respectively. The participants were weighed with light clothes and without shoes. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). Height and BMI were expressed as standard deviation scores (SDS) by Child Growth Standards from World Health Organization. Predicted adult height was calculated by a median of parents' heights + 6.5 cm.

Central precocious puberty was defined as a boy younger than 9 years with the development of secondary sexual characteristics (testicular volume >4 ml), increased height velocity, advanced bone age, and pubertal-luteinizing hormone (LH) response to gonadorelin stimulation test (LH peak >5 IU/1).[12]

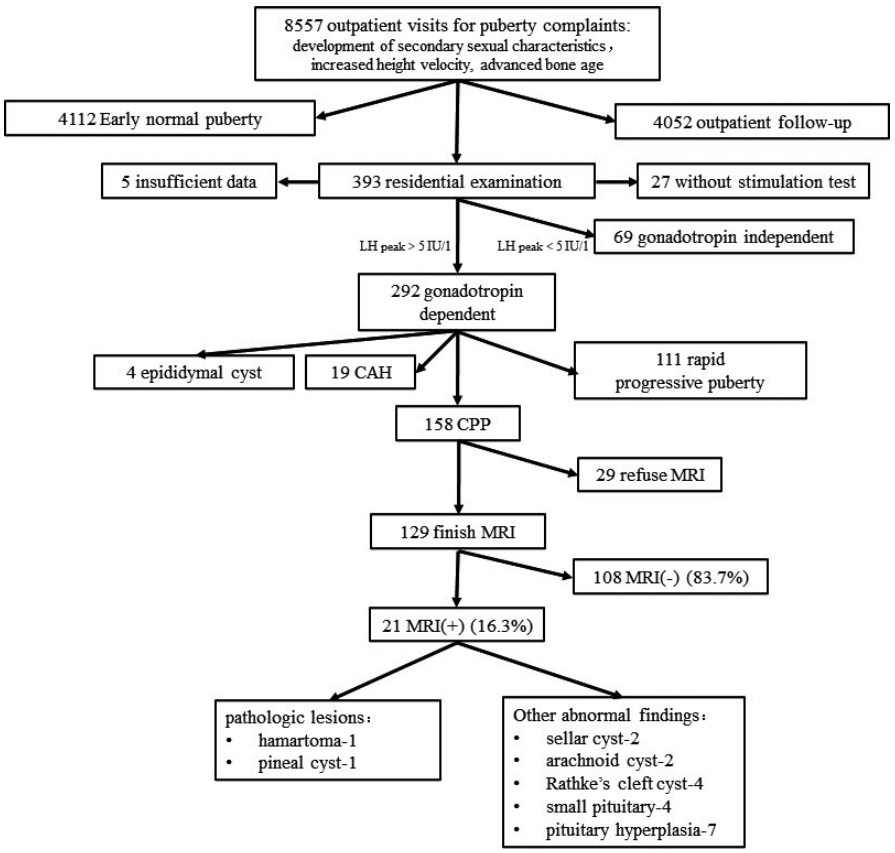

FIGURE 1 Inclusion procedure of male CPP cohort

TABLE 1 Demographic and clinical characteristics of enrolled CPP boys in China

	Total (*n* = 129)	MRI(-) (*n* = 108)	MRI (+) (*n* = 21)	*p* value
Clinical parameters				
Age at diagnosis (years)	9.40 ± 0.75	9.38 ± 0.80	9.51 ± 0.47	.470
Height-SDS	1.13 ± 0.99	1.18 ± 1.02	0.93 ± 0.78	.293
BMI-SDS	1.33 ± 0.92	1.39 ± 0.92	1.02 ± 0.92	.090
Predicted height	167.2 ± 20.5	168.3 ± 16.1	161.7 ± 35.7	.417
Tanner stage				
G (2/3/4/5)	38/73/13/5	32/64/10/2	6/9/3/3	.078
PH(1/2/3/4/5)	65/62/4/1/0	56/52/2/1/0	9/10/2/0/0	.302
Laboratory features				
Basal LH (IU/l)	1.77 ± 1.08	1.77 ± 1.10	1.77 ± 1.00	.976
Basal FSH (IU/l)	3.38 ± 1.93	3.39 ± 1.99	3.32 ± 1.64	.890
Peak LH at GnRH stimulation (IU/l)	22.9 ± 8.36	22.62 ± 8.45	24.17 ± 7.90	.438
Peak FSH at GnRH stimulation (IU/l)	9.75 ± 6.20	9.64 ± 5.96	10.34 ± 7.47	.635
Ratio at GnRH stimulation (IU/l)	3.15 ± 2.18	3.19 ± 2.29	2.96 ± 1.49	.659

Venous blood samples were obtained to measure the concentrations of follicular stimulating hormone (FSH) and luteinizing hormone (LH). The gonadotropin releasing hormone stimulation test was performed by measuring serum LH and FSH levels at 0, 30, 45, 60 and 90 min of intervals after an intravenous bolus administration of LH-releasing hormone (2.5–3 μg/kg, maximum 100 ug, Triptorelin Acetate, Ipsen Pharma Biotech). Plasma thyroxin and thyroid-stimulating hormone (TSH) concentrations were also measured to exclude hypothyroidism.

The brain MRI examination was performed with Philips Achieva, 3.0 Tesla magnet, Philips Medical Systems.

2.4 | Statistical analyses

Statistical analyses were performed using SPSS version 23.0 (IBM Corp., Armonk, NY, USA). Descriptive statistics for the continuous variables were expressed as mean ± standard deviation. Student *t* test was used to compare the different characteristics for continuous variables. One-way ANOVA was used to compare differences in proportions for categorical variables. Chi-square test for trend was used to compare numbers and incidence between groups categorized by years. A probability value less than 0.05 was considered as statistically significant.

3 | RESULTS

One hundred and twenty nine boys were included in our single-centre study. The mean chronological age at diagnosis was 9.40 ± 0.75 years, and the youngest patient was 6.42 years old. Penis and testis enlargement, voice break, pubic hair and axillary hair growth were the most common complaints. According to the Tanner stages of pubertal maturation, 28.7% of the subjects were at G2, 55.6% were at G3, 10.1% were at G4, and 3.9% were at G5. More information about the auxological and laboratory data is presented in Table 1.

Normal MRIs were found in 108/129 CPP boys (83.7%) and can be classified as idiopathic (MRI negative [-]) (Figure 1). There were 21 (16.3%) with abnormal findings (MRI positive (+) cases), mostly in the area of the pituitary, and included 4 Rathke's cleft cyst, 4 small pituitary, 7 pituitary hyperplasia, 2 sellar cyst and 2 arachnoid cyst. Only one patient, an 8.8-year-old boy with a hypothalamic hamartoma, had a lesion typically associated with CPP. Another had a (φ4.9 mm) pineal cyst and a normal hCG level which may have represented a non–hCG-secreting germinoma. No patient had CNS-related symptoms or comorbid hydrocephalus, and none required biopsy or surgery.

No significant difference was found between MRI (+) and MRI (-) cases in terms of clinical features, including age of puberty onset (Table 1). The age of all the MRI (+) cases was >8 years (Table 2), and there was no statistical difference on incidence among them. There

TABLE 2 Age distribution of CPP cases

Age(year)	MRI(+) cases	CPP cases	%
<7	0	3	0
<8	0	4	0
<9	4	22	18
<10	12	72	17
≥10	5	28	18

TABLE 3 Annual period of patients diagnosed with CPP

Year	2011–2012	2013–2014	2015–2016	2017–2018	2019
CPP cases	19	13	31	38	28
MRI (+) cases	2	2	4	10	3
Incidental findings	10.5%	15.4%	12.9%	26.3%	10.7%

was a slight increase in the number of boys diagnosed with CPP from 2011 to 2019 (p <.05). The annual distribution of patients is shown in Table 3. The incidence of finding intracranial lesions was ranged from 10.5% to 26.3% (p =.383). Indeed, there was no change in the ratio of MRI (+) CPP cases but the number of CPP boys significantly increased from 2011 to 2019.

4 | DISCUSSION

Previous studies have reported high prevalence of brain lesions observed in CPP boys, and therefore, it has been strongly recommended that a brain MRI be performed in all cases.[11,13] However, our 9 years of data from Chinese National Clinical Research Center for Child Health revealed that brain lesions were not the major cause of male CPP in China.

The majority had minor findings in the pituitary region which might not be typically associated with CPP. No gliomas or astrocytoma, the tumours most commonly associated with CPP, was found in our study. An American cohort study reported that 64% of boys had neurogenic CPP with neurofibromatosis type I being the most common disorder.[14] A study from Turkey revealed that 26% boys have organic CPP and most CPP boys above the age of 7 years were idiopathic.[10] Based on small population studies from Italy, 40%[7] male CPP cases showed neurogenic causes. Likewise, a study from France reported that the incidence of organic CPP cases was 73% and 53% of them were associated with a previously treated CNS lesions.[15] In the current study, patients with previously treated CNS lesions or neurofibromatosis were excluded, and therefore, the incidence of abnormal and likely pathologic brain lesions in male CPP patients was the lowest compared with previous literature.

We are the first to report the incidence of brain lesions in Chinese CPP boys. We found that most cases had normal MRIs and of the 16.3% with abnormalities, only 1 was definitely pathogenic. Our results were consistent with a Korean study where they reported 7% CPP boys with brain lesions and 93% boys with idiopathic CPP.[16] In boys, majority of the organic cases had been diagnosed before the age of 7 years.[10] Because the youngest case in our series was 6.4 years old, we are unable to comment on the frequency of abnormal MRIs in CPP boys under age 7. In our study, intracranial abnormal lesions were found in 16.3% but none except for the boy with a hamartoma were considered causative of CPP. However, hypothalamic hamartoma and other brain tumours accounted for the main causes of Caucasian CPP cases among Europe and America.[4,9,17] We recommend further studies to unveil the differences among nations or regions.

The number of male CPP cases diagnosed in our centre increases with time. In consistence to our results, a recent study reported that the incidence of CPP cases increased from 2011 onward in France.[18] A previous epidemiologic study published in 2013 revealed that 1.74% of Chinese boys showed a testicular volume of 4 ml or more before 9 years of age, and the average age of puberty onset in boys was 7.4 ± 0.28 years in East China.[19] With the economic development, children' dietary habits and nutritional status also changed in China. Obesity is positively associated with the sexual maturation in males.[20] Our data found an increase in overall CCP cases in which majority of the cases were idiopathic. Although no consensus has been reached on the influence of obesity on male sexual maturation, the BMI-SDS of all CPP cases were obviously above the normal average.

No distinguished clinical features or laboratory findings between MRI(+) and MRI(-) groups were found in the current study. Ayfer et al (2015) reported that CPP patients with organic causes showed higher testosterone and LH peak levels at younger age with reduced final height.[10] Another study found that patients with CNS lesions were diagnosed at lower Tanner stages.[14] More specific studies should be carried out to distinguish clinical and biochemical features of CPP boys with intracranial lesions.

Brain MRI scan was routinely offered at our centre for all the boys diagnosed with CPP to identify the previously unseen intracranial lesions or potential abnormalities. Previous study found that pituitary size and shape were correlated with the hormonal profile and CPP patients with advanced bone age had a tendency towards a greater pituitary length.[21] While many centres may still see a need for MRIs in all CPP boys, our study suggests main cause for Chinese CPP boys was idiopathic and the yield of findings which require intervention in asymptomatic boys is very low, so routine MRIs might be withheld. These findings need to be confirmed with contemporary studies in CPP boys from other parts of the world including Europe and America.

However, we might underestimate the frequency of brain lesions because patients with known brain lesions before or during the follow-up were excluded in our study. Participants in our cohort were mostly from east China, so the prevalence of brain lesions in CPP boys among the other parts of China is needed which will help to know the ethnic or region factors influencing brain lesions and CPP. Moreover, long-time follow-ups are necessary to monitor further impact of organic causes on puberty onset and progression.

In conclusion, there is an increasing trend of male CPP over the last decade in China. While MRI abnormalities were found in 16.3%, cases associated with pathogenic brain lesions were uncommon, which clearly differs from what other studies from different parts of the world have reported in the past.

CONFLICT OF INTEREST

The authors declare that there is no financial or nonfinancial conflict of interest relevant to this work.

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AUTHOR CONTRIBUTION

Junfen Fu contributed to the conception of this manuscript. Shumin Zhan and Jinling Wang contributed to the data acquisition and data analyses. Jinling Wang drafted the manuscript. Shumin Zhan and Rahim Ullah critically revised the manuscript for important intellectual content. Jinna Yuan contributed to the data interpretation. Guanping Dong, Wei Wu and Ke Huang contributed to the clinical evaluation of precocious puberty in Chinese boys.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study may be available on reasonable request from the corresponding author.

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