

# Incidental Findings on Brain Magnetic Resonance Imaging in Children with Central Precocious Puberty

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**Objectives:** To investigate brain magnetic resonance imaging (MRI) findings in patients with central precocious puberty (CPP) by age at onset and sex.

**Methods:** We included 130 CPP patients with brain MRI findings of the pituitary gland treated at Ewha Womans University Mokdong Hospital between February 2007 and October 2013 and divided them by age and sex: boys, girls aged ≤6 years, and girls aged >6 years. The control group comprised 224 patients who underwent brain MRIs, and we compared their incidental brain findings with those of the CPP group.

**Results:** In the CPP subgroups who underwent pituitary MRIs, the frequency of incidental brain lesions was 31.6% in boys, 47.1% in girls ≤6 years and 29.8% in girls >6 years. The incidence of pituitary abnormalities was 42.1% in boys, 64.7% in girls ≤6 years and 47.9% in girls >6 years. Among pituitary abnormalities, pituitary hypoplasia had a significantly higher incidence rate in girls ≤6 years (41.2%) than in boys (15.8%) or girls >6 years (13.8%,  $P=0.027$ ). Hypothalamic hamartomas were detected in one girl aged ≤6 years and in one boy, but not in girls aged >6 years ( $P=0.075$ ). The incidence of pineal cysts was higher in the CPP groups and significantly higher in girls ≤6 years (47.1%) than in the control group (11.2%,  $P=0.001$ ).

**Conclusion:** There was a higher incidence of brain abnormalities on pituitary MRIs and a higher incidence of pineal cysts, possibly associated with CPP pathogenesis, in younger CPP patients than in other patients. (**Ewha Med J 2020;43(4):53-59**)

Received June 25, 2020

Revised July 30, 2020

Accepted August 24, 2020

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## Key Words

Precocious puberty; Pituitary hypoplasia; Pineal cyst

## Introduction

Precocious puberty is a condition that has both important and diverse consequences for the affected children and their families, and it imposes both physical and psychological impacts on the patients. The disease can potentially follow a sudden, dynamic course. Therefore, early diagnosis can facilitate an understanding of the prospective disease course with regard to the rate of pubertal progression, development of stature, bone age progression, reproductive development, psychosocial adjustment, and good health [1]. Central precocious puberty

(CPP) refers to the premature activation of the HPG (hypothalamic-pituitary-gonadal) axis, with consequent early development of secondary sexual characteristics. The age criteria of normal and precocious puberty are controversial; however, the cutoffs that are routinely used to diagnose CPP are set at the age of 8 and 9 years for girls and boys, respectively [2,3]. Basic clinical examinations are important for CPP diagnosis, although there is an increasing awareness of the importance of imaging to detect secondary causes of CPP. In all cases of progressive CPP, a magnetic resonance imaging (MRI) of the brain should be conducted to determine whether a hypothalamic or

pituitary lesion is present [4,5]. In children with CPP, the incidence of such lesions is higher in boys (40%–90%) than in girls (8%–33%), which decreases further (less than 2%, in one series) when puberty begins after age 6 in girls [5–7]. Nonetheless, neoplastic causes of precocious puberty, although uncommon, are important etiologic factors in precocious sexual development, and early, rapid recognition of these rare presentations is important [8]. A higher incidence of central nervous system (CNS) lesions in boys with CPP has been noted previously, and brain imaging is routinely undertaken in boys. Thus, brain MRI is recommended in all boys and girls younger than 6 years with CPP [9].

This study was conducted to investigate the brain MRI findings of patients with CPP to identify the incidence of pituitary abnormalities and incidental lesions. Furthermore, the study intended to clarify the need for MRI testing on the basis of the criteria defined by the specific characteristics of the MRI abnormalities as well as a consideration of the possible CPP-related findings among MRI incidental lesions compared with those in the control group.

## Methods

### 1. Ethics statement

This was a retrospective study, and it was approved by the institutional review board of the Ewha Womans University Mokdong Hospital (EUMC2016-06-023-0055). Informed consent was waived due to the retrospective nature of the study.

### 2. Study population

We undertook a retrospective case-control study to review and analysis of radiologic findings in patients diagnosed with CPP. We obtained a list of patients who were diagnosed with CPP between February 2007 and October 2013 at the Ewha Womans University Mokdong Hospital, Seoul, Korea. Among the children diagnosed with CPP, a total of CPP patients who underwent pituitary MRI were included. All patients younger than 6 years underwent MRI exam, and patients aged 6 or older were included in the post-test study if they had symptoms such as headaches or at the parent's preference.

In a study of patients stored as CPP in the National Classifications of Disease from 2008 to 2014, a total of 37,890 girls

and 1,220 boys were diagnosed with CPP [10]. The overall incidence of CPP was confirmed to be 122.8 per 100,000 persons (girls, 262.8; boys, 7.0). In this study, for the patients diagnosed with CPP from February 2007 to October 2013 and who had their MRI taken, the retrospective data collection was set for a study period of approximately 7 years. During this period, the patients diagnosed with CPP were examined. In terms of overall CPP incidence, calculations were made for 354 patients, composed of 224 control patients and 130 CPP patients, among the children who visited our hospital for the pediatric premature evaluation.

The hormone levels were analyzed for the determination of a CPP diagnosis, and the positive criteria were as follows. Non-fasting venous blood samples were obtained to measure the concentrations of follicular stimulating hormone (FSH) and luteinizing hormone (LH). The detection limits for LH and FSH were 0.05 and 0.06 IU/L, respectively. Serum LH and FSH levels were measured at 0, 30, 45, 60, and 90 minutes after an intravenous bolus administration of LH-releasing hormone (synthetic gonadotropin releasing hormone [GnRH]; 100  $\mu$ g Relefact, Sanofi-Aventis, Frankfurt am Main, Germany) [11]. We defined CPP by peak LH level  $>5$  IU/L, or stimulated FSH/LH ratio  $>0.66$  IU/L. If the GnRH stimulation test was not conducted, the hormone level was considered pubertal if the basal LH level exceeded 0.3 IU/L.

We included girls with breast development before age 8 and a diagnosis of CPP. Positive results on the GnRH stimulation test and bone age advancement were considered manifestations of CPP for girls before age 8 and boys before age 9 [12,13]. The CPP patients were assigned to 3 groups by age and sex as specified: boys, girls aged  $\leq 6$  years, and girls aged  $>6$  years.

The control group comprised the patients who underwent brain MRI at the same ages as the CPP group to enable a comparison of incidental brain findings. The control group included patients without pathological abnormalities and CPP and whose brain MRI conducted between February 2007 and October 2013 for symptoms of headaches, seizures, etc., and showed normal results.

Patients with previously known abnormalities, associated endocrine disorders, previous hormonal therapies, malformation, neurofibromatosis, or other genetic conditions, including congenital adrenal hyperplasia, were excluded from the study.

### 3. Grouping of MRI findings

For the purposes of this study, the study population was further stratified on the basis of MRI abnormalities into four categories: Category 1 comprised participants with normal MRI; Category 2 included patients with incidental findings, such as, pineal cysts, arachnoid cysts, choroid plexus cysts, and subependymal heterotopia; Category 3 included patients who had fine lesions in the pituitary gland, such as hyperplasia, hypoplasia, Rathke's cleft cyst, or adenoma; and Category 4 included participants with pathological lesions, such as hamartoma.

### 4. Measurement of the pituitary gland

There are two methods to determine pituitary hypoplasia or hyperplasia. One option is to objectively and directly measure the height of the pituitary gland, whereas the other considers the shape of the pituitary gland. With the method that uses

objective parameters, the reference may be insufficient and reliability may be compromised. Therefore, pituitary hypoplasia or hyperplasia was determined by both, objective and subjective, parameters in a previous study [14,15]. The objective parameters are not commonly used in pediatric patients, but the standard values are set at 4.9–6.5 mm in the sagittal plane, and the subjective parameters are graded in accordance with whether the shape of the gland is convex or concave on the sagittal imaging diagnosis [14,15].

### 5. Statistical analyses and radiologic diagnostic criterion

Statistical analyses were performed using IBM SPSS Statistics ver. 22.0 (IBM Co., Armonk, NY, USA). Continuous variables were expressed as mean  $\pm$  standard deviation. An independent t-test was used to compare the CPP groups and the control group. The chi-square test was used to determine whether

**Table 1.** Comparisons of prevalence of incidental findings, pituitary abnormalities and pathologic magnetic resonance imaging findings in central precocious puberty groups

	Group 1 (boys)	Group 2 (girls $\leq$ 6 yr)	Group 3 (girls >6 yr)	Control	P-value
Central precocious puberty					
No. of patients	19	17	94	224	
Age (yr)	8.53 $\pm$ 1.93	5.2 $\pm$ 1.3	7.54 $\pm$ 0.56	6.95 $\pm$ 0.84	
Magnetic resonance imaging features					
Category 1: normal	7 (36.8)	3 (17.6)	44 (46.8)	-	
Category 2: incidental findings					
Pineal cyst	4 (21.1)	8 (47.1)*	23 (24.5)*	25 (11.2)	<0.001
Arachnoid cyst	1 (5.3)	0 (0)	5 (5.3)	8 (3.6)	0.698
Choroid plexus cyst	1 (5.3)	0 (0)	0 (0)	0 (0)	0.102
Subependymal heterotopia	0 (0)	0 (0)	1 (1.1)	0 (0)	0.367
Total	6 (31.6)	8 (47.1)*	28 (29.8)*	33 (14.7)	<0.001
Category 3: pituitary abnormality					
Hyperplasia	4 (21.1)	3 (17.6)	25 (26.6)	-	0.762
Hypoplasia	3 (15.8)	7 (41.2) <sup>†</sup>	13 (13.8)	-	0.027
Rathke's cleft cyst	1 (5.3)	1 (5.9)	6 (6.4)	-	>0.99
Pituitary adenoma	0 (0)	1 (1.1)	0 (0)	-	>0.99
Total	8 (42.1)	11 (64.7)	45 (47.9)	-	0.353
Category 4: pathologic findings					
Hypothalamic hamartoma	1 (5.3)	1 (5.9)	0 (0)	-	0.075

Values are presented as mean  $\pm$  standard deviation or number (%).

\*P<0.05 vs. control.

<sup>†</sup>P<0.05 vs. >6 years.

there was a statistically significant difference between the CPP groups. Statistical significance was defined as  $P < 0.05$ .

All radiological diagnoses were diagnosed by a qualified radiologist. Among them, the criteria for diagnostic imaging of arachnoid cyst and pineal cyst were as follows. The arachnoid cyst was identified by imaging for extra-axial lesions, with similar signal intensity as that of the cerebrospinal fluid, in all sequences of the MRI. In the case of the pineal cyst, the diagnosis was made when the signal intensity was shown on MRI T1-weighted image or in T2-weighted image or was slightly higher than cerebrospinal fluid [16].

## Results

The study included a total of 354 participants. The CPP group comprised 130 children (19 boys [mean age, 8.53 years], 17 girls aged  $\leq 6$  years [mean age, 5.2 years], and 94 girls aged  $> 6$  years [mean age, 7.54 years]). The control group included 224 children (mean age, 6.95 years) (Table 1).

The CPP group with the normal MRI brain findings comprised seven boys, three girls aged  $\leq 6$  years, and 44 girls aged  $> 6$  years. The incidence of normal brain findings in the CPP groups was 31.6% among the boys, 17.6% in the girls aged  $\leq 6$  years, and 46.8% in the girls aged  $> 6$  years. The incidence of incidental brain findings in the CPP groups was 31.6% among boys, 47.1% in girls aged  $\leq 6$  years, and 29.8% in girls aged  $> 6$  years, and no significant between-group differences were observed for the CPP groups. The incidence of incidental brain findings in the control group was 14.7%, which was significantly lower than in the CPP groups ( $P < 0.001$ ). Intergroup comparisons showed a significantly higher incidence among the

girls than in the control group ( $P < 0.05$  vs. control) (Table 2).

The incidence of pineal cyst in the control group was 11.2% lower than in the CPP groups. Intergroup comparisons showed that the incidence of pineal cyst was 47.1% for the CPP group of girls aged  $\leq 6$  years and 24.5% in the CPP group with girls aged  $> 6$  years, and was significantly higher than in the control group (11.2%,  $P < 0.001$ ) (Table 2). However, there was no significant between-group difference in the incidence of arachnoid cysts, choroid plexus cysts, and subependymal heterotopia in the CPP groups, nor when compared with the control group (Table 2).

With regard to pituitary abnormalities, there was no significant intergroup difference (64.7% in girls aged  $\leq 6$  years, 47.9% in girls aged  $> 6$  years, and 42.1% in boys with CPP;  $P < 0.353$ ) and the incidence of pituitary hyperplasia, pituitary hypoplasia, Rathke's cleft cyst, and pituitary adenoma were compared among the three groups. The incidence of pituitary

**Table 3.** Comparisons of prevalence of pituitary abnormalities and pathologic findings of pituitary magnetic resonance imaging among central precocious puberty groups

	Girls		Boys	P-value
	$\leq 6$ yr	$> 6$ yr		
Pituitary abnormalities	11 (64.7)	45 (47.9)	8 (42.1)	0.353
Hyperplasia	3 (17.6)	25 (26.6)	4 (21.1)	0.762
Hypoplasia	7 (41.2)*	13 (13.8)	3 (15.8)	0.027
Rathke's cleft cyst	1 (5.9)	6 (6.4)	1 (5.3)	$> 0.99$
Pituitary adenoma	0 (0)	1 (1.1)	0 (0)	$> 0.99$
Pathologic findings				
Hamartoma	1 (5.9)	0 (0)	1 (5.3)	0.075

Values are presented as number (%).

\* $P < 0.05$  vs.  $> 6$  years.

**Table 2.** Comparisons of prevalence of incidental brain magnetic resonance imaging findings in central precocious puberty groups vs. control group

	Girls		Boys	Control	P-value
	$\leq 6$ yr	$> 6$ yr			
Total incidental findings	8 (47.1)*	28 (29.8)*	6 (31.6)	33 (14.7)	$< 0.001$
Pineal cyst	8 (47.1)*	23 (24.5)*	4 (21.1)	25 (11.2)	$< 0.001$
Arachnoid cyst	0 (0)	5 (5.3)	1 (5.3)	8 (3.6)	0.698
Choroid plexus cyst	0 (0)	0 (0)	1 (5.3)	0 (0)	0.102
Subependymal hypertrophy	0 (0)	1 (1.1)	0.0	0 (0)	0.367

Values are presented as number (%).

\* $P < 0.05$  vs. control.

hypoplasia (41.2% in girls aged  $\leq 6$  years, 13.8% in girls aged  $>6$  years, and 15.8% in boys) differed significantly between the three CPP groups ( $P=0.027$ ) (Table 3). Hypothalamic hamartomas were detected in one girl aged  $\leq 6$  years (5.9%) and in one boy (5.3%), but not in girls aged 6 years ( $P=0.075$ ).

## Discussion

Recent studies have reported an increase in the incidence of CPP, especially the incidence of idiopathic CPP [17,18]. Besides the development of specific tests for the diagnosis, history taking, and physical examination, brain-imaging modalities have become an important diagnostic tool in CPP. However, brain MRI screening in patients with CPP remains controversial.

In a study by Mogensen et al. [19] in a CPP population in Denmark, most cases were idiopathic; 13 out of 208 girls (6.3%) with early or precocious puberty and no other CNS symptoms were found to have pathological CNS lesions on the MRI, which were connected with CPP. All 13 girls were  $>6$  years of age, and 6 girls were in the age range of 8–9 years. A high proportion of girls in the of 6–8-year age range with early or precocious development had pathological findings on brain MRI. In the 6- to 8-year-old girls with early or precocious development, pathological causes were identified on the brain MRI that could not have been detected from a clinical investigation in this study. Thus, the findings of this study indicate that girls with precocious pubertal development of central origin before 8 years of age should be screened by using brain MRI [19]. However, another study conducted in Italy in 2014 in 182 girls showed 86% had no specific findings on the brain MRI; 11% had incidental findings unrelated with CPP, and 3% reported hamartomas. In contrast to previous studies, routine screening with brain MRI is not recommended in all girls with CPP between 6 and 8 years of age [20]. Against this background, we investigated the brain MRI findings of CPP patients and found pituitary abnormalities and incidental brain findings on the brain MRI examination.

In our study, the total incidences of incidental brain findings, including pineal cysts, arachnoid cysts, choroid plexus cysts, and subependymal heterotopia, were compared between CPP groups without any significant differences. However, comparison with the control group showed significantly higher incidences in the CPP groups, with girls  $\leq 6$  years showing the

highest incidences.

Melatonin, which is released from the pineal gland, is considered responsible for puberty, although the exact mechanism has not been defined [21]. Pineal cysts, which have a prevalence rate of 0.6% in the pediatric population, are well-known asymptomatic incidental findings, but have been associated with CPP [22–25]. Similarly, in the present study, the incidence of pineal cysts was significantly higher in the CPP group than in the control group, which showed normal MRI findings, especially in girls aged  $\leq 6$  years with CPP. This suggests that pineal cysts may be considered an incidental brain lesion with regard to CPP pathogenesis. However, only the data on brain MRIs, excluding the hormone serum level, were obtained in the control group of our study; therefore, it was difficult to clearly compare the prevalence of pituitary abnormalities between the CPP groups and the control group.

The proportion of diseases related to CNS diseases is higher in boys, but must also be excluded in girls. Approximately 95% of girls with CPP have idiopathic CPP and only 5% have CPP arising from a secondary cause. However, more than 50% of boys with CPP have an identifiable etiology, and idiopathic CPP is a diagnosis of exclusion [26]. In the present study, we expected that incidental brain findings would be significantly higher than the control group in boys with CPP, but no statistical significance was found for higher incidental brain findings in boys with CPP. However, it should be considered that the number of boys included in this study was too small to generate a significant difference with the control group. Hamartoma, also known as brain lesion, as the cause of CPP was identified in only two in our study population (one in a girl aged  $\leq 6$  years, one in a boy), but there was no significant difference. In general, many articles have reported that hamartomas are a common brain lesion in patients with CPP. Faizah et al. [27] reported that hypothalamic hamartoma was the commonest tumor causing CPP in their patients, accounting for 10 out of 34 (29%) cases with abnormal findings on brain imaging.

This data analysis has some limitations, which should be considered with regard to the clinical interpretation of the findings. First, the number of boys with CPP who were included in this study was insufficient for a proper analysis and did not result in significant intergroup results on comparative analysis. Second, the CPP groups performed the pituitary MRI and the control group performed the brain MRI. In general, the meth-

ods of image acquisition of the pituitary MRI and the brain MRI are different. The pituitary MRI creates high resolution images that allow physicians to see the pituitary region better, and bias was included according to the inspection protocol. In the control group, only the brain MRI was performed and the hormone tests not undertaken. Therefore, it was difficult to clearly compare the incidence of the pituitary gland abnormalities and the pineal cysts between the CPP and control groups. Third, we did not define the control group as 'healthy control' which could have provided selection bias. In addition, there was no data of the control group for pituitary abnormalities. Finally, as we examined only Korean children, it is possible that the regional prevalence of brain lesions in CPP patients is related to the study population, race, and healthcare and insurance systems.

In conclusion, this study suggests that pituitary MRIs are necessary as a diagnostic tool in CPPs, especially in young girls and boys. Children with CPP are more likely to have incidental findings on brain MRI. In particular, the relatively high incidence of MRI findings in the CPP group than in the control group suggests the possibility that pineal cysts, which were considered to be an incidental finding on brain MRI, may be related to the CPP pathogenesis. There is a need to further elucidate the brain MRI features of the CPP diagnosis in future large-sample research studies that include rigorous statistical analysis.

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