Clinical Pediatric Endocrinology

Vol.32 / No.1
January 2023
pp 58–64

Original Article

Increased frequency of central precocious puberty during the coronavirus disease (COVID-19) pandemic at a single center in the Osaka Metropolitan Area of Japan

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Highlights

- Frequency of CPP increased during the COVID-19 pandemic at a single center.
- The proportion of girls with CPP increased from 11% to 19% in the outpatient clinic.
- Clinical features of patients with CPP during the pandemic did not change.

Abstract. As environmental factors are known to affect the timing of puberty, self-isolation during the coronavirus disease (COVID-19) pandemic may affect the incidence of central precocious puberty (CPP). This study aimed to evaluate the frequency of CPP during the COVID-19 pandemic at a single center in the Osaka metropolitan area of Japan. We retrospectively analyzed the annual frequency of CPP occurrence before and after the first declaration of COVID-19 state of emergency in Japan at our hospital. We performed an interrupted time-series analysis to investigate the frequency of patients with CPP at our hospital from 2016 to 2021. There was a significant increase in the frequency of patients with CPP before and after the state of emergency declaration, both overall and among females. However, there was no significant increase in the number of males. There were no significant differences in the clinical, auxological, and endocrinological features between those diagnosed before and after the state of emergency. Overall, the frequency of CPP significantly increased during the COVID-19 pandemic at a single center in the Osaka metropolitan area of Japan.

Key words: precocious puberty, coronavirus disease, pandemic

Received: January 31, 2022 Accepted: October 24, 2022 Advanced Epub: December 20, 2022
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Introduction

In December 2019, the severe acute respiratory syndrome coronavirus 2 causing coronavirus disease (COVID-19) spread worldwide (1, 2), prompting the World Health Organization to declare a global pandemic on March 11, 2020 (3). In Japan, the first COVID-19 outbreak occurred in February 2020, and the government declared the first COVID-19 state of emergency from April 7 to May 25, 2020 (4). Instead of a national lockdown, as observed in many parts of Europe and the United States, the Prime Minister of Japan requested that Japanese individuals refrain from unnecessary outings and that businesses refrain from hosting events, parties, and other such activities (5). Furthermore, in Osaka, the governor requested temporary closure of elementary, junior high, and high schools from March to May 2020. Consequently, the Japanese people started to self-isolate.

During the COVID-19 pandemic, there was an increase in the number of outpatient consultations for suspected precocious puberty and patients diagnosed with central precocious puberty (CPP). The timing of puberty is influenced by several environmental factors such as weight, childhood dietary habits, physical activity, psychological factors, and/or exposure to electromagnetic fields (6–10), some of which contribute to the onset of CPP (11, 12).

Therefore, in this study, we investigated the frequency of CPP before and after the declaration of the COVID-19 state of emergency in the Osaka Metropolitan Area of Japan.

Materials and Methods

Study design

This retrospective study was conducted to retrieve data from 2016 to 2021 on the number of patients with CPP and their clinical features from the medical records of the Division of Pediatric Endocrinology and Metabolism, Children's Medical Center, Osaka City General Hospital. This hospital is one of two children's hospitals in the Osaka metropolitan area, covering a population of approximately 8 million. The data of patients with CPP from April 7, 2019 to April 6, 2020 (one year before the first COVID-19 state of emergency in Japan, defined as the "Before COVID-19 pandemic" group) were compared to those from April 7, 2020 to April 6, 2021 (one year after the state first COVID-19 state of emergency, defined as the "After COVID-19 pandemic" group). The frequency of patients with CPP for the past four years was also investigated for comparison by interrupted times series (ITS) analysis (the "2016" group included patients between April 7, 2016 to April 6, 2017; "2017" group, April 7, 2017 to April 6, 2018; "2018" group, April 7, 2018, to April 6, 2019). The frequency of outpatients with endocrine diseases other than CPP was also retrieved from 2016 to 2021. This study was approved by the institutional review board of Osaka City General Hospital (No. 2112118).

Participants

Among the patients referred to our center for suspected precocious puberty and diagnosed with CPP four years before or one year after the first COVID-19 state of emergency in Japan (between April 7, 2016, and April 6, 2021), those aged ≥ 3 and < 13 yr were selected for this study. CPP was diagnosed according to the diagnostic criteria for Japanese patients (13) based on both symptomatic and endocrinological findings. The symptoms for diagnosis were as follows: for girls, breast development at < 7 yr and 6 mo of age, pubic hair development, labia minora pigmentation or axillary hair development at < 8 yr of age, and menarche at < 10 yr and 6 mo of age; for boys, testicular, penile, or scrotal development at < 9 yr of age; pubic hair development at < 10 yr of age; axillary hair, beard development, or voice break at < 11 yr of age. Additionally, an early growth spurt and advanced bone age were considered signs of precocious puberty if the timing of pubertal onset was unclear. Endocrinological laboratory findings for the diagnosis were: basal LH value ≥ 0.5 mIU/mL or peak LH value ≥ 5.0 mIU/mL at the time of GnRH stimulation test. Patients were excluded from this study if they had congenital hypothalamic-pituitary malformations, intracranial space-occupying lesions, chromosomal abnormalities, severe motor and intellectual disabilities, Graves' disease, small-for-gestational-age short stature, or were undergoing treatment with medications that may interfere with pubertal development.

Measurements

We retrieved data on age at diagnosis, sex, height, weight, and body mass index (BMI) by chart review. Height and BMI were standardized for chronological age by conversion to standard deviation score (SDS) values. For girls, if available, we retrieved clinical data including the Tanner scale of breast development at diagnosis, chronological age at Tanner breast stage 2 (B2), opportunity for detection (school physical checkup or not), bone age, and endocrinological data such as LH, FSH, E2, and peak LH at GnRH stimulation. Plasma LH, FSH, and E2 levels were measured using an electrochemiluminescence immunoassay (Roche Diagnostics International Ltd., Tokyo, Japan).

Statistical analysis

All statistical data were analyzed using Easy R version 1.54 (Saitama Medical Center, Jichi Medical University, Saitama, Japan) (14). A Poisson regression model was created with the number of patient occurrences per month as the dependent variable and elapsed time since April 7, 2016 (period), declaration of the state of emergency (emergency), and duration of the emergency

doi: 10.1297/cpe.32.2022-0008

(duration of emergency) as independent variables. The total number of patients per month in the Division of Pediatric Endocrinology and Metabolism at Osaka City General Medical Center was included in the model as an offset term to adjust for the effect of an increase or decrease in the total number of patients. Analyses were performed for all boys and girls. The statistical significance of continuous variable comparisons was assessed using the Mann–Whitney U test. Categorical variables were compared using the chi-square test or Fisher's exact test if the expected cell size was small (< 5). Differences were considered statistically significant at a p-value < 0.05.

Results

The number and proportion of patients diagnosed with CPP after the first COVID-19 state of emergency almost doubled from 7.3% (33/452) to 14.3% (63/441) in outpatient clinics ($p < 0.005$) (**Table 1**). When compared by sex, the proportion of girls with CPP significantly increased from 11.3% (28/248) to 18.8% (51/271) ($p = 0.02$), and that of boys also increased from 2.5% (5/204) to 7.1% (12/170) ($p = 0.04$) between the before COVID-19 pandemic group and After COVID-19 pandemic group. However, ITS analysis showed a significant difference in the frequency of CPP cases before and after the state of emergency declaration, both overall and for girls, but not for boys (**Figs. 1 and 2**). As for other endocrine diseases, the proportion of patients with growth impairment decreased significantly from 31.0% (77/248) to 21.8% (59/271) between the two groups ($p = 0.02$). However, among boys, the number of patients with growth impairment was not significantly different between the two groups. Additionally, the proportion of patients with thyroid disease was not significantly different between the two groups in both overall comparisons and by sex. ITS analysis showed no significant difference in the frequency of growth impairment and thyroid disease in patients before and after the state of emergency. Data on growth impairment and thyroid diseases are shown in Supplementary Figs. 1–4.

There were no significant differences in chronological age at diagnosis, height SDS, or BMI SDS between the two groups in the overall, female, and male comparisons (**Table 2**). Additionally, chronological age at Tanner stage B2, chronological age at diagnosis, Tanner stage at diagnosis, opportunity for detection, bone age, difference between chronological age and bone age, and endocrinological test results in female patients with CPP did not differ significantly between the before and after COVID-19 pandemic groups (**Table 3**).

Discussion

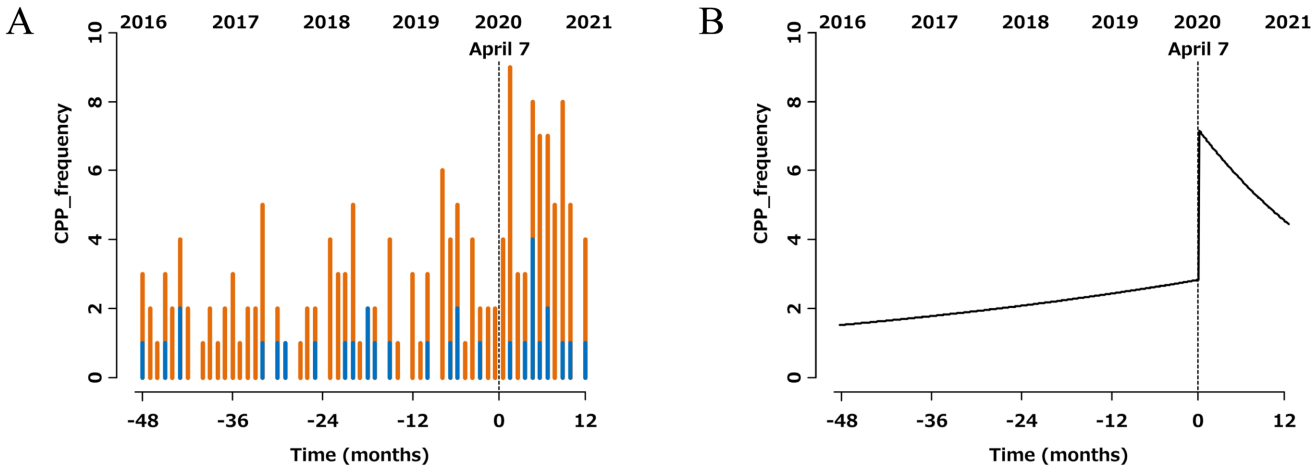
To the best of our knowledge, this is the first report to show an increased CPP frequency during the COVID-19 pandemic in Japan. ITS analysis demonstrated a significant increase in the frequency of CPP in all cases and in girls, although there was no increase in boys after the state of emergency declaration at a single center. Our results are consistent with those of Stagi *et al.*, who demonstrated an increased incidence of CPP in girls during the lockdown in Italy (10). However, the incidence of CPP has increased in recent decades, despite the COVID-19 pandemic. A Danish population-based study reported a 6-fold increase in the yearly incidence of CPP from 2.6 per 10,000 to 14.6 per 10,000, during

Table 1. Number and proportion of outpatients with central precocious puberty (CPP) and other endocrine diseases

		2016–2017		2017–2018		2018–2019		2019–2020		2020–2021		Ratio between 2019–2020 and 2020–2021 (%)	p-value
		N	P (%)	N	P (%)	N	P (%)	N	P (%)	N	P (%)		
Total	All patients	512	–	504	–	434	–	452	–	441	–	–	–
	CPP	23	4.5	21	4.2	25	5.8	33	7.3	63	14.3	195.7	< 0.005
	Growth impairment	179	35.0	204	40.5	140	32.3	145	32.1	128	29.0	90.5	0.06
	Thyroid disease	57	11.1	47	9.3	37	8.5	35	7.7	31	7.0	90.8	0.78
	Other	253	49.4	232	46.0	232	53.5	239	52.9	219	49.7	93.9	0.37
Girls	All patients	260	–	272	–	241	–	248	–	271	–	–	–
	CPP	19	7.3	17	6.3	19	7.9	28	11.3	51	18.8	166.7	0.02
	Growth impairment	63	24.2	91	33.5	66	27.4	77	31.0	59	21.8	70.1	0.02
	Thyroid disease	32	12.3	30	11.0	24	10.0	20	8.1	20	7.4	91.5	0.90
	Other	146	56.2	134	49.3	132	54.8	123	49.6	141	52.0	104.9	0.64
Boys	All patients	252	–	232	–	193	–	204	–	170	–	–	–
	CPP	4	1.6	4	1.7	6	3.1	5	2.5	12	7.1	288.0	0.04
	Growth impairment	116	46.0	113	48.7	74	38.3	68	33.3	69	40.6	121.8	0.18
	Thyroid disease	25	9.9	17	7.3	13	6.7	15	7.4	11	6.5	88.0	0.90
	Other	107	42.5	98	42.2	100	51.8	116	56.9	78	45.9	80.7	0.04

N, number; P, proportion.

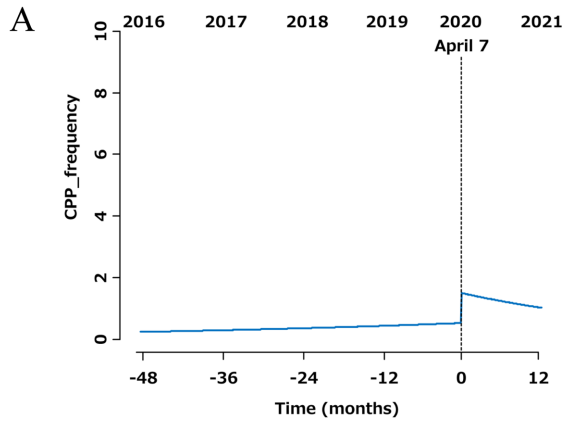
doi: 10.1297/cpe.32.2022-0008



C

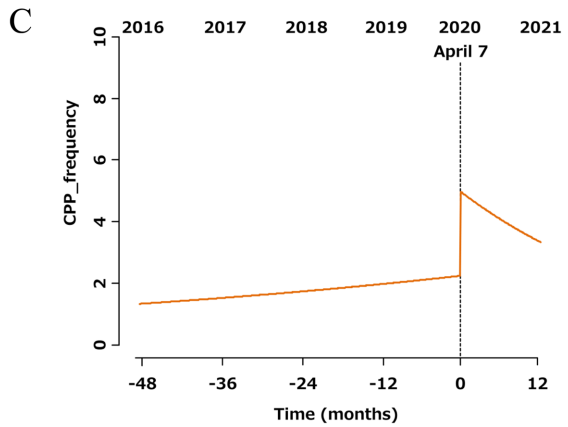
	Estimate	StdErr	exp(Est.)	lower	upper	*p*
(Intercept)	-3.246	0.212	0.039	0.026	0.059	0.000
Period	0.013	0.007	1.013	0.999	1.027	0.073
Emergency	0.930	0.326	2.535	1.338	4.805	0.004
Duration Emergency	-0.053	0.039	0.949	0.878	1.024	0.179

Fig. 1. (A) Monthly frequency of patients with central precocious puberty (CPP) in Osaka City General Hospital from 2016 to 2021. (B) Interrupted time-series analysis in all patients with CPP. (C) Regression model parameters of the interrupted time-series analysis in all patients with CPP. StdErr, standard error; Exp, exponential.



B

	Estimate	StdErr	exp(Est.)	lower	upper	*p*
(Intercept)	-4.222	0.491	0.015	0.006	0.038	0.000
Period	0.016	0.017	1.016	0.983	1.050	0.346
Emergency	1.026	0.764	2.791	0.624	12.480	0.179
Duration Emergency	-0.047	0.089	0.954	0.801	1.135	0.594



D

	Estimate	StdErr	exp(Est.)	lower	upper	*p*
(Intercept)	-2.779	0.236	0.062	0.039	0.099	0.000
Period	0.011	0.008	1.011	0.995	1.027	0.179
Emergency	0.798	0.361	2.220	1.093	4.509	0.027
Duration Emergency	-0.044	0.044	0.957	0.878	1.043	0.314

Fig. 2. (A) Interrupted time-series analysis in male patients with central precocious puberty (CPP). (B) Regression model parameters of the interrupted time-series analysis in male patients with CPP. StdErr, standard error; Exp, exponential. (C) Interrupted time-series analysis in female patients with CPP. (D) Regression model parameters of the interrupted time-series analysis in female patients with CPP. StdErr, standard error; Exp, exponential.

doi: 10.1297/cpe.32.2022-0008

Table 2. The chronological age at diagnosis and the auxological data of patients with central precocious puberty

	Variables	before COVID-19 pandemic	after COVID-19 pandemic	*p*-value
Total	Chronological age at diagnosis (yr)	9.0 [8.6–9.7]	8.8 [8.0–9.8]	0.31
	Height SDS	1.1 [0.5–1.5]	1.1 [0.4–1.7]	0.95
	BMI SDS	0.6 [0.1–1.1]	0.5 [0.0–1.0]	0.73
Girls	Chronological age at diagnosis (yr)	9.0 [8.3–9.5]	8.5 [7.9–9.0]	0.07
	Height SDS	1.1 [0.4–1.5]	1.1 [0.4–1.8]	0.83
	BMI SDS	0.6 [0.1–1.2]	0.6 [0.3–1.1]	0.96
Boys	Chronological age at diagnosis (yr)	11.2 [10.8–11.7]	11.3 [10.8–11.6]	0.67
	Height SDS	0.9 [0.5–1.3]	0.7 [0.4–1.4]	0.51
	BMI SDS	0.4 [0.1–0.7]	0.2 [–0.1–0.5]	0.33

The data are shown as the medians [interquartile range]. BMI, body mass index; COVID–19, coronavirus disease; SDS, standard deviation score.

Table 3. Clinical data and endocrinological test results in female patients with central precocious puberty

Variables	before COVID-19 pandemic	after COVID-19 pandemic	*p*-value
Chronological age at B2 (yr)	7.5 [6.9–8.5]	7.3 [6.5–7.8]	0.16
Chronological age at diagnosis (yr)	9.0 [8.3–9.5]	8.5 [7.9–9.0]	0.07
Time from B2 to diagnosis (yr)	1.0 [0.5–2.1]	0.8 [0.4–1.3]	0.47
The opportunity of detection (%)			
School physical checkup	7.1	3.9	0.61
Tanner breast stage at diagnosis (%)			0.47
Stage 2	19.6	28.6	0.53
Stage 3	64.7	57.1	0.67
Stage 4	15.7	14.3	1.00
Bone age (yr)	11.0 [10.1–12.0]	10.3 [9.3–11.7]	0.14
Bone age minus chronological age (yr)	2.0 [1.6–2.5]	1.8 [1.2–2.6]	0.67
Basal LH (mIU/mL)	1.9 [0.4–4.7]	1.6 [0.6–3.6]	0.84
Basal FSH (mIU/mL)	3.7 [2.5–6.2]	4.6 [2.9–5.8]	0.89
Basal E2 (pg/mL)	21.4 [5.0–45.8]	22.9 [6.9–39.6]	1.00
Peak LH at GnRH stimulation (mIU/mL)	10.5 [9.5–18.3]	14.5 [8.0–17.8]	0.81

The data are shown as the medians [interquartile ranges]. B2, Tanner stage breast 2; COVID-19, coronavirus disease.

the 20 years between 1998 and 2017 (11). In addition, a Korean national study demonstrated that the annual incidence of CPP in girls increased 4.7-fold from 2008 to 2014 (from 89.4 to 415.3 per 100,000 population) (12). Compared with the reported increases in CPP and those over the previous 4 years (2016 to 2019) at our center, our findings show that the number of patients with CPP increased steeply during the COVID-19 pandemic.

The frequency of CPP among girls was higher than among boys in this study. Similarly, another report found a higher frequency of CPP in girls than in boys (15). Environmental factors are known to differentially affect pubertal onset according to sex. For example, the influence of adiposity on pubertal timing remains controversial in boys, with obesity associated with both early and late pubertal onset (16, 17). Additionally, the first sign of pubertal development in boys is an increase in testicular volume; however, such changes can be more difficult to observe by parents. Therefore, CPP in boys was less likely to be detected, resulting in a small sample size and possibly insufficient data. Our data did not reveal the impact of the COVID-19 pandemic on CPP onset in boys.

Regarding other endocrine diseases, the frequency of girls with growth impairment decreased significantly between the two groups. However, this decrease was not large compared with the change in frequency over the past several years, and the state of emergency declaration did not significantly influence the frequency of growth impairment in the ITS analysis. Although this decrease might be relevant to an earlier pubertal onset or growth spurt in the general population, it is difficult to determine the relevance because our data were limited, and the timing of pubertal onset in patients other than patients with CPP was not investigated. Therefore, the timing of pubertal onset in patients other than those with CPP during the COVID-19 pandemic should be investigated in future studies.

Although we did not analyze the factors that increased the frequency of CPP, two possible underlying mechanisms are considered: 1) the effects of environmental factors or 2) an increase in the opportunity for early detection of CPP rather than an actual increase in the number of patients with CPP. First, many environmental factors contribute to CPP onset. Some potential mechanisms, including obesity,

doi: 10.1297/cpe.32.2022-0008

childhood nutrition, physical activity, psychological factors, and overuse of electronic devices, are known to affect pubertal timing (6–10). Studies have shown that the prevalence of obesity and symptoms of depression and anxiety have increased, while the time spent on sports activities has significantly decreased among children during the COVID-19 pandemic (18–20). An Italian study also demonstrated increased use of electronic devices and accelerated pubertal progression in patients with CPP during the lockdown, hypothesizing that the overuse of electronic devices could influence the timing of puberty (10). Additionally, other studies have reported that the timing of pubertal onset is associated with international adoption, traumatic or stressful events, and child abuse (9, 21, 22), which supports the possibility that a rapid change in a child's social situation could affect the onset of CPP. Second, there is a possibility that it is the chance of early detection of CPP that has increased rather than an actual increase in the number of patients with CPP. The average delay between the observation of signs of puberty by the parents and the final diagnosis of CPP was previously reported to be 1.5 yr in a Belgian study, and 7 mo (range, 0–66 mo) in a Danish study (23, 24). More time spent with parents after the state of emergency might have made it easier to identify patients with possible CPP, leading to more timely medical consultation. As the COVID-19 pandemic reduced the number of patients with other infectious diseases (25), it is also possible that physicians had more time to notice the signs of early puberty and to make a referral to a pediatric endocrinologist. However, we could not show evidence for this hypothesis because there was no significant difference between the patients before and after the state of emergency declaration regarding the time from the appearance of B2 to CPP diagnosis (**Table 3**). Additionally, we could not detect the impact of school physical checkups on this change in the proportion of CPP, although growth curves have been used in checkups since 2016 in Japan.

In our study, there were no significant differences in chronological age at B2 and at diagnosis, auxological data, endocrinological test results, or other clinical data between the two groups among girls. These data suggest that the characteristics of patients with CPP did not change, although the proportion of patients with CPP increased during the COVID-19 pandemic. However, Stagi *et al*. reported that in Italy, patients with CPP had an earlier chronological age at B2 and diagnosis, and their basal and peak LH values increased during and after the lockdown for COVID-19 compared to the previous 5 years (10). Although the reasons for the differences between our study and this previous report are unclear, differences in race might be partially involved. For example, Biro *et al*. showed that pubertal onset occurs later in Asian girls than in Caucasian girls in the United States (26).

This study has several limitations. First, it was a single-center study and not a population-based study. Second, we did not assess factors that may have influenced the pubertal timing of CPP frequency. Finally, we did not adjust for ascertainment bias in physicians who referred the patients to us. Therefore, further multicenter investigations are required to confirm the impact of the COVID-19 pandemic on the incidence of CPP and pubertal onset.

Conclusion

The frequency of CPP significantly increased during the COVID-19 pandemic at a single center in the Osaka metropolitan area of Japan, although the underlying mechanisms still need to be determined. To our knowledge, this is the first report to show an increased CPP frequency during the COVID-19 pandemic in Japan.

Conflict of interests: The authors declare no conflict of interest.

Acknowledgments

We would like to thank Jun Mori for fruitful discussions and Hirotsugu Yasuda for his support in statistical analysis.

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doi: 10.1297/cpe.32.2022-0008

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