Status of Central Precocious Puberty Cases at the Onset of Coronavirus Disease 2019 Pandemic: A Single-Center Experience

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What is already known on this topic?
The timing of puberty in children is emerging at increasingly earlier ages. During the COVID-19 pandemic, children experienced epidemiologic changes such as stress, sedentary lifestyle, and weight gain.

What this study adds on this topic?
The most important finding of our study is the age of admission, stage of puberty, and the age at initiation of treatment with the diagnosis of CPP during the pandemic period were earlier.

ABSTRACT
Objective: The onset of puberty in children is occurring at an increasingly earlier ages. During the coronavirus 2019 pandemic, children experienced epidemic-related changes such as stress, sedentary lifestyle, and weight gain.

Materials and Methods:Auxological, clinical, endocrinological, and radiological data in the files of 57 patients who were given gonadotropin-releasing hormone analog therapy with the diagnosis of central precocious puberty between April 1 and July 1, 2019 (group 1) and April 1 and July 1, 2020 (group 2) were analyzed retrospectively.

Results: A total of 27 patients (26 girls, 1 boy) in group 1 and 30 patients (28 girls, 2 boys) in group 2 were diagnosed with central precocious puberty. Mean ages at diagnosis for groups 1 and 2 were 28.54 ± 0.94 and 7.92 ± 0.96 years, respectively (P = .018). Mean bone age at diagnosis for group 1 was 9.78 ± 1.48 (6.8-12), and for group 2 it was 8.78 ± 1.11 (6.5-12) years (P = .013).

The mean age of starting treatment in groups 1 and 2 was 8.94 ± 0.17 (6.8-9.8) and 8.07 ± 0.02 (5.8-10) years, respectively (P = .002). Average birth weights for groups 1 and 2 were 950 ± 1100 (2300-3400) and 3180 ± 717 (870-3820) g, respectively (P = .012). Treatment was started when breast stage was T3 in 57.69% of group 1 and T2 in 75% of group 2, and a statistical difference was found between them (P = .006) and uterine length was higher in group 2 (P = .144).

Conclusion: During the coronavirus 2019 pandemic, patients who start central precocious puberty therapy were of younger age. In our single-center experience, coronavirus 2019 was not seen to have a significant impact on central precocious puberty.

Keywords: COVID-19, pandemic, central precocious puberty

INTRODUCTION
Puberty is a period when psychosocial maturation and secondary sexual characteristics are formed. For girls, breast development and for boys, increase in testicular size are the first pubertal findings. Central precocious puberty (CPP) is the onset of secondary sexual characteristics before the age of 8 in girls and 9 in boys, with the activation of the hypothalamic-pituitary-gonadal axis and the pulsation of gonadotropin-releasing hormone (GnRH). The frequency of CPP is 1/5000-10 000. Early puberty, with rapid skeletal development and premature closure of the epiphyses, causes children to be shorter in final height compared to their genetic potential. The coronavirus 2019 (COVID-19) pandemic has caused significant changes in our country as well as in the whole world. The first case in our country was seen in March 2020. After this date, restrictions started and schools closed for 3 months. This caused lifestyle changes

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in children and the time spent at home was increased. Factors such as staying at home for a long time, psychological stress, online education and increased use of electronic devices, sedentary lifestyle, and weight gain might have affected puberty. For these reasons, we aimed to evaluate the status of CPP cases during lockdown in our study.

We observed changes in the frequency and age of admission of cases who applied to our clinic at the beginning of the COVID-19 pandemic who were diagnosed with CPP and given GnRH analog therapy. In this study, we aimed to compare the CPP cases treated during the pandemic period with the CPP cases treated the previous year and to evaluate the clinical features of these cases.

MATERIALS AND METHODS

Type of Study
This study is a retrospective evaluation of the file information of 57 patients who were diagnosed with CPP and started GnRH analog therapy between April 1 to July 1, 2019, and April 1 to July 1, 2020, at Dr. Sami Ulus Maternity and Children’s Health and Diseases Research and Training Hospital, Pediatric Endocrinology Clinic. They were categorized as groups 1 and 2, respectively.

Data Collection and Analysis
From the file records of the cases, gender, age at presentation (AP), puberty stage (Tanner-Marshall), height (cm), body weight (kg), body mass index (BMI) (kg/m²) and standard deviation score (SDS), bone age (BA), basal follicle-stimulating hormone (FSH), basal LH, E2, total testosterone, peak FSH and LH response to LHRH test, long diameter of the uterus, and prepubertal or pubertal ovarian volumes according to pelvic ultrasonography were evaluated using reference values for Turkish children.5

Inclusion Criteria
Testicular volume was measured with an orchidometer, and volume of 4 mL and above was considered pubertal. Uterine long diameter ≥35mm, ovarian long diameter ≥20 mm were considered pubertal. Precocious puberty diagnostic criteria are that breast development starts before the age of 8 in girls, testicular volume was 4 mL or above before the age of 9 in boys, basal LH value measured by ICMA is above 0.3 IU/L, and GnRH stimulation test LH peak was over 5 IU/L/7,8

Exclusion Criteria
Patients with known endocrinological problems and patients with organic lesions on cranial magnetic resonance imaging were excluded from the study.

Statistical Analysis
All statistical analyses were performed using the Statistical Package for the Social Sciences 20.0 (SPSS Inc., Chicago, Ill, USA) program. For continuous variables, the Shapiro–Wilk test was used to check whether they are normally distributed. After the normality test, descriptive statistics were presented as mean ± standard deviation and minimum and maximum values for the continuous variables and as a percentage for categorical variables. Student’s t test was used to compare the groups for continuous variables for normally distributed variables, while Mann-Whitney U test for non-normal distributed variables. Fisher’s exact test was performed to determine the relationship between categorical variables. In addition, 2-proportion Z test was used to compare for group proportions. The results were evaluated at a 95% CI, and the P value was considered significant at <.05.

Ethics
Health Sciences University–Dr. Sami Ulus Maternity and Children’s Health and Diseases Research and Training Hospital Institutional Review Board reviewed and approved the protocol of the study (2021/06–200). Verbal and written informed consent was obtained from patients’ parents.

RESULTS
A total of 57 patients who were diagnosed with CPP and started GnRH analog therapy from April 1 to July 1, 2019, and April 1 to July 1, 2020, were included in the study. The cases that started treatment in 2019 were defined as group 1, and the cases that started treatment in 2020 during the COVID-19 period were defined as group 2. The number of patients in group 1 was 27 (26 girls, 1 boy), and the number of patients in group 2 was 30 (28 girls, 2 boys) (P = .617).

Testicular volume of 1 male patient in group 1 was found to be 6 mL, and the total testosterone level was 106.69 ng/dL. Testicular volumes of 2 male patients in group 2 were 4 mL and 4 mL, respectively, and total testosterone levels were 10 ng/dL and 10.55 ng/dL. The mean AP was 8.54 ± 0.94 (6.8-9.8) in group 1, 7.92 ± 0.96 (5.7-10) in group 2, and there was a statistical difference between them (P = .018). The mean difference between the BA and the chronological age of group 1 was 1.24 ± 1.00 (−0.1 to 2.2) years, the mean difference between group 2 was 0.86 ± 0.77 (−0.7 to 2.2) years (P = .024). While the age of initiation of treatment was 8.94 ± 1.00 (6.8-9.8) years in group 1, it was 8.07 ± 0.02 (5.8-10) years in group 2, and a significant difference was found between groups (P = .002). It was observed that the mean birth weight of group 1 was 2950 ± 1100 (2300-3400) g, group 2 was 3180 ± 717 (870-3820) g, and a statistically significant difference was found between the groups. (P = .012). While the height SDS of group 1 was 0.89 ± 1.14 (−1.58 to 2.93), it was 0.56 ± 1.04 (−1.38 to 2.49) in group 2, and there was no significant difference between them (P = .258). There was a statistical significance between the groups in terms of Tanner breast stages (P = .006). An important point about this is group 1 patients presented with T3 (57.69%) most and group 2 patients presented with T2 (75%) most. Demographic and anthropometric properties of the patients are given in Tables 1 and 2, and laboratory and radiological findings and clinical properties of the patients are given in Tables 3 and 4, respectively.
DISCUSSION

As a result of our study, we found that the age of admission, puberty stage, and the age at the beginning of treatment after the diagnosis of CPP during the pandemic period were earlier. These results suggest that during the COVID-19 period, the pubertal findings of the patients were noticed earlier by their families and they reached the hospital earlier, or maybe only as being more concerning, younger cases came during pandemic and the less concerned patients stayed home, making a statistically significant difference. Although there is no significant difference in terms of the follow-up period, it is noteworthy that the time between symptom onset and initiation of treatment is shorter in the COVID-19 period. More careful clinical observation may have been made as the applications to health centers decreased.

Central precocious puberty is frequently seen in girls and their incidence is lower in boys. Similarly, the number of male cases was found to be less in our study.

In a study, it was found that CPP cases increased and pubertal progression accelerated during the COVID-19 period, and it was thought that this situation might be triggered by environmental factors (such as BMI, electronic device use). In another study, an increase in the frequency of precocious puberty cases was found during the COVID-19 period, but it was stated that large cohorts were needed for a definite opinion on this issue.

These results suggest that genetic and environmental factors are effective in the onset and progression of puberty. In our study, there was no increase in CPP cases during the initial period of COVID-19.

While the time of puberty in humans is 70-80% dependent on genetic factors, environmental factors are also effective. In a study, it has been hypothesized that the onset of pubertal development is due to increased BMI, excessive use of electronic devices, and psychological triggering. Nutritional factors are thought to play a key role in the onset of puberty. Early puberty may develop in relation to nutrition. It has been reported in previous studies that obese children have an early age at menarche.

It is thought that the lockdowns during the pandemic caused movement restriction and more calories to be taken. In our study, the BMI SDS values of the cases in the pandemic period were found to be similar to the previous year.

The COVID-19 period is likely to affect children’s mental health with the infection itself, anxiety, and social distance. School closures, reduced social relationships, changes in daily habits, and parents’ concerns about financial issues and other problems can affect children emotionally. There are opinions suggesting that psychological factors may also be important in the onset and course of puberty.

As a result of our study, we found that admissions due to precocious puberty did not increase at the beginning of the pandemic, but the patients were diagnosed at an earlier age and treatment was started at an earlier age and with a shorter stature.

There are some limitations to our study. First, our data were collected for 3 months only, which caused our sample size to be small. That is because we thought CPP might have been affected by the lockdown lifestyle. As children stayed at home, they become more sedentary, gained weight, used more electronic devices, and were under psychological stress. We tried to find a relation between this lifestyle and CPP; therefore, we only included 3 months of lockdown and compared this timeline with the past year’s same months. Comparing this situation with the period of March to July 2020 and March to July 2021 may give more accurate results. Therefore, the results of the study are insufficient to show the effects of the pandemic and longer-term studies are needed.

Another limitation of our study is the fact that the cases were evaluated retrospectively, and their physical examination, BA,
and ultrasonography were evaluated by different physicians. In our study, the average daily calorie intake and physical activity status of the patients were not compared with the period before the pandemic, but the data were interpreted considering the possible changes expected due to the applied restrictions.

**CONCLUSION**

In conclusion, the most important finding of our study is the early admission age in patients who were given treatment for precocious puberty. This may have been due to changes in the lifestyle and psychological effects of children during the pandemic period, as well as to the other factors that we do not know clearly at the moment. New studies on this subject will be useful in terms of evaluating possible factors in the timing and course of puberty. A new study is planned with a larger group with a longer follow-up period on this subject.

**The Take-Home Messages**

The timing of puberty in children is emerging at increasingly earlier ages. During the COVID-19 pandemic, children experienced epidemic-related changes such as stress, sedentary lifestyle, and weight gain. Due to these changes in the pandemic, we did not detect an increase in the number of precocious puberty at the onset of COVID-19 in our planned study.

**Ethics Committee Approval:** This study was approved by the Ethics Committee of Health Sciences University–Dr. Sami Ulus Maternity and Children’s Health and Diseases Research and Training Hospital (Approval No: 2021/06-200).

**Informed Consent:** Verbal and written informed consent was obtained from patients’ parents.

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