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Changing Etiological Trends in Male Precocious Puberty: Evaluation of 100 Cases with Central Precocious Puberty over the Last Decade

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Key Words
Central precocious puberty · Males · Etiological factors

Abstract
Background/Aims: There are few studies in the literature that have evaluated the etiological factors in boys with central precocious puberty (CPP), and these studies are limited in terms of the sample size. In the present study, we aimed to evaluate the etiological factors in male CPP cases. ***Methods:*** One hundred male CPP subjects, aged between 9 months and 10.5 years, were included. The medical records were screened, and age at diagnosis, bone age, body weight, height, pubertal stage, imaging findings of the pituitary gland, testosterone, and basal and stimulated gonadotropin levels were recorded. ***Results:*** There was no underlying cause in 74% of the cases, and an organic cause was determined in only 26%. Most of the organic cases had been diagnosed before the age of 7 years, whereas most of the idiopathic cases had been diagnosed after the age of 7 years. ***Conclusion:*** An organic cause was determined in 26% of the male patients with CPP. This rate is one of the lowest rates in the literature and indicates that the number of idiopathic male CPP cases is increasing over time. When a boy is diagnosed with CPP above the age of 7 years, the odds of detecting an underlying pathology are very low, and these cases are mostly idiopathic.

Introduction

The activation of the gonadotropin-releasing hormone (GnRH) pulse generator before the age of 8 years in girls and 9 years in boys results in central precocious puberty (CPP). In contrast to girls, an underlying central nervous system (CNS) lesion is present in the majority of the CPP cases in boys; thus, CNS imaging is strongly suggested in all boys presenting with CPP. There are few studies in the literature that have evaluated the etiological factors in boys with CPP, and these studies are limited in terms of the study population. Most of them were carried out before the year 2000. According to these studies, the prevalence of an underlying organic cause in male CPP cases has been reported to range between 73 and 94% [1, 2]. On the other hand, studies after the year 2000 have reported a wide range for the prevalence of male organic CPP cases (25–83%) [3–6]. The number of cases in most of these studies is considerably low as they include only 10–20 cases. There are no recent studies that reflect the current state of knowledge in the etiological evaluation of CPP in boys. In the present study, we aimed to evaluate the etiological factors in male CPP cases and to analyze the distribution of cases by year to find out whether there has been an increase in the number of idiopathic cases in recent years.

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Material and Methods

Patients

The medical records of 100 boys with CPP who were treated with GnRH analogs between the years 2003 and 2014 were retrospectively analyzed. Age at admission, chronological age at diagnosis, height age, bone age, body weight, height, pubertal stage, paternal and maternal height, imaging findings of pituitary gland, testosterone, and basal and stimulated gonadotropin levels were recorded. The boys who had testicular enlargement (≥4 ml) before 9 years of age with a peak luteinizing hormone (LH) level ≥5 IU/l during GnRH stimulation test and a testosterone level ≥0.3 ng/ml were considered CPP cases [7–9]. GnRH testing was performed in every patient. Blood samples were collected at minute 0 for follicle stimulating hormone (FSH) and LH measurements, and then the patients were intravenously administered 100 μg of GnRH (gonadorelin acetate, Ferring®). Following drug administration, blood samples were collected at 20, 40, 60, and 120 min for FSH and LH measurement. Pituitary MRI was performed in every patient after the diagnosis of CPP.

The patients' body weights were measured with a digital body weighing scale, and height measurements were performed in the standing position with a Harpenden stadiometer by a personnel trained in height measurement and auxology. CDC (Centers for Disease Control and Prevention) growth charts were used to interpret the growth data [10], which were represented as standard deviation scores (height-SDS). The body mass index (BMI) was calculated using the formula weight in kg/height in meters squared. BMI-SDS were calculated according to the LMS method by using the CDC charts [11]. Pubertal staging was carried out using Marshall and Tanner staging [12]. A Prader orchidometer was used to measure the volume of the testicles. The bone age was evaluated using the Greulich and Pyle method [13].

Basal FSH, LH, and testosterone levels were analyzed in blood samples collected between 8:00 and 8:30 a.m. The immunochemiluminometric assay (ICMA) method using commercial kits (ARCHITECT System, Abbott Laboratory Diagnostics, USA) was used to measure FSH and LH levels. The sensitivity of the FSH and LH assays was 0.3 and 0.07 IU/l, respectively. Serum testosterone levels were measured using the ICMA method on an IMMULITE 2000 System (Siemens, UK) using a commercial kit.

Statistical Analysis

SPSS for Windows 11.5 software was used for the analysis of the data. Descriptive statistics for the continuous variables were expressed as mean ± standard deviation. The importance of difference between the groups in terms of the mean values was analyzed using the Student t test when there were 2 independent groups. p values <0.05 were considered statistically significant.

Results

One hundred boys, who were followed up for CPP at a single center between 2003 and 2014, were included in the study. The mean chronological age at diagnosis was 7.7 ± 1.9 years. The youngest patient was 9 months old, whereas the oldest was 10.5 years old. The mean bone age at diagnosis was 9.1 ± 1.7 years. The mean age at the onset of complaints was 6.8 ± 1.7 years. Pubic hair growth was the most frequent complaint (65.1%) followed by penis enlargement (18.6%) and axillary hair growth (9.3%). Changes in behavior such as increase in aggressiveness were present in 70% of the cases. When categorized according to their pubertal stage, 35.9% of the subjects were at Tanner stage G2 (genitalia), 30.8% were at stage G3, and 33.3% were at stage G4 at diagnosis. Pubic hair stages also ranged from P2 to P4. The auxological data and the laboratory results at the time of diagnosis are presented in table 1.

CNS imaging of the cases showed no pathological findings in 74% (74/100), and these cases were diagnosed with idiopathic CPP. Pathological findings on MRI were observed in 26 cases (26%), and these cases were classified as organic CPP. Space-occupying lesions were observed in 20 out of the 26 cases with an organic pathology, while developmental anomalies of CNS were present in 6 cases. Space-occupying lesions included hamartoma (5/20), microadenoma (3/20), arachnoid cyst (8/20), optic glioma (2/20), craniopharyngioma (1/20), and pineal germinoma (1/20). Comorbid hydrocephaly was observed in the 8 patients with an arachnoid cyst. Attention deficit and hyperactivity were observed in 4 idiopathic CPP cases with normal MRI findings. In 3 cases, there were microadenomas of 3, 5, and 6 mm in size, and the hormonal evaluation of these cases was normal except for gonadotropin levels. One of the cases had pineal germinoma, and as his hCG level was normal, it was considered a non-hCG-secreting germinoma. Eleven of the CPP cases were followed up and treated for different diseases at the time of diagnosis. The six patients with developmental anomalies of CNS showed signs of epilepsy and mental-motor retardation on follow-up and were treated with antiepileptic drugs at the time of diagnosis of CPP. Five cases of arachnoid cysts with accompanying hydrocephalus were diagnosed with CPP during their follow-up.

When the cases were divided into 4 groups by year (2003–2005, 2006–2008, 2009–2011, and 2012–2014), it was observed that the number of cases increased until 2009 and then maintained its high ratio thereafter in the last 5 years. Idiopathic CPP cases were found to be mainly responsible for this increase since the number of organic CPP cases in each of the 4 groups was similar (6, 6, 7, and 7 cases, respectively). Twenty-one of the 26 organic cases (80.8%) had been diagnosed before the age of 7 years, and 60 of the 74 idiopathic cases (81.1%) had been diagnosed after the age of 7 years. Sixty percent of the cases who had been diagnosed with CPP before the age of 7 years had an underlying organic cause, whereas 92% of

Table 1. Auxological data and the laboratory results at the time of diagnosis

Auxological parameters	
Age at diagnosis, years	7.7±1.9
Age at onset of symptoms, years	6.8±1.7
Height age, years	8.2±2.3
Bone age, years	9.1±1.7
Height-SDS	0.6±0.4
BMI-SDS	1.2±0.5
Height-SDS for bone age	−0.9±0.8
Bone age/chronological age ratio	1.2±0.1
Target height, cm	171.2±3.5
Predicted adult height, cm	160.5±3.5
Target height-SDS	−0.8±0.5
Predicted adult height-SDS	−2.3±0.6
Laboratory results	
Basal FSH, IU/l	2.9±1.5 (0.7–5.2)
Basal LH, IU/l	1.5±0.9 (0.3–3.6)
Basal testosterone, ng/ml	1.3±0.9 (0.3–2.5)
Peak LH at GnRH stimulation, IU/l	15.2±7.8 (5.0–29.2)

Values are expressed as means ± standard deviation (ranges).

Table 2. Etiology of CPP according to referral period and patient age

	Organic cases	Idiopathic cases	All cases
Referral period			
2003–2005	6 (66.7%)	3 (33.3%)	9 (100%)
2006–2008	6 (35.3%)	11 (64.7%)	17 (100%)
2009–2011	7 (19.4%)	29 (80.6%)	36 (100%)
2012–2014	7 (18.4%)	31 (81.6%)	38 (100%)
All years	26 (26%)	74 (74%)	100 (100%)
Patient age at diagnosis, years			
<7	21 (60%)	14 (40%)	35 (100%)
≥7	5 (8%)	60 (92%)	65 (100%)

the cases who had been diagnosed after the age of 7 years were idiopathic (table 2).

When the idiopathic CPP cases were compared with the organic CPP cases, the organic CPP cases were observed to be diagnosed at an earlier age and to have a more advanced bone age. Basal testosterone levels and peak LH levels in the GnRH test were higher in the organic CPP cases (table 3).

Discussion

Recent studies have shown that the onset of puberty in girls has shifted toward a younger age and that especially the number of idiopathic CPP cases has increased [14]. It is not clear whether it is also true for male CPP cases since there are not enough studies available. The present study showed that the number of male CPP cases has gradually increased in the last 10 years. Since the number of organic CPP cases has not changed with the years, the idiopathic CPP cases were mainly responsible for this increase.

In our study, an underlying organic cause or developmental anomalies of CNS were observed in overall 26% of the cases. This rate is one of the lowest rates in the literature. Similar to the present study, Rizzo et al. [3] found that an underlying organic cause was present in 25% of the cases; however, while Rizzo et al. [3] evaluated only 12 male CPP cases, in the present study, 100 male cases were evaluated, which makes this study one of the most comprehensive studies with respect to the number of cases. The study by De Sanctis et al. [15], which included 45 cases, found that the incidence of organic cases was 40%, while this rate is 48.7% in the review by Pigneur et al. [16]. In our study, MRI showed that 77% of the cases with an organic pathology had space-occupying lesions, while 23% of the cases had developmental anomalies of CNS. The most common space-occupying lesion was arachnoid cyst with comorbid hydrocephalus, while hamartoma was the second most common. In 11 of the cases with an underlying organic pathology, there was a known CNS lesion, whereas the others were first diagnosed with CPP, and then an underlying organic lesion was detected on MRI. If only the cases with an organic lesion detected on MRI after the diagnosis of CPP were included, the number of organic cases would be much lower, and the prevalence of organic forms of CPP would be underestimated. The results are reliable and reflect more accurately the percentage of absolute organic cases in CPP patients since all the organic cases were included regardless of the time of detection of the underlying organic lesion. It should always be kept in mind that there is a significant amount of patients with a CNS lesion who are diagnosed with CPP during follow-up [17].

In this study, the amount of organic cases remained the same throughout the years, whereas the number of idiopathic cases increased until 2009 and then maintained its high ratio thereafter. External reasons for this increase such as better awareness of CPP among local physicians and better access to specialized care cannot be excluded. Besides, in the last 10 years, as a result of the common use of media such as television and the internet, there might have been an increase in the parents' knowledge about early puberty and in the willingness to seek medical advice. Since this is not an epidemiologic popula-

Table 3. Comparison of clinical and laboratory features between idiopathic CPP cases and organic CPP cases in boys

	Idiopathic cases	Organic cases	p value
Clinical parameters			
Age at diagnosis, years	8.6±1.1	5.2±1.4	<0.001
Age at onset of symptoms, years	7.6±0.9	4.6±1.4	<0.001
Height age, years	9.1±1.6	5.6±1.7	<0.001
Bone age, years	9.8±1.2	7.2±1.3	<0.001
Height-SDS	0.6±0.3	0.6±0.4	0.79
Height-SDS for bone age	−0.5±0.4	−1.9±0.9	<0.001
BMI-SDS	1.5±0.6	0.4±0.3	<0.001
Target height, cm	171.0±3.4	171.7±3.9	0.44
Target height-SDS	−0.8±0.5	−0.7±0.6	0.44
Predicted adult height, cm	161.4±2.9	157.9±3.8	<0.001
Predicted adult height-SDS	−2.2±0.5	−2.7±0.6	<0.001
Laboratory features			
Basal FSH, IU/l	2.9±1.6	3.1±1.4	0.55
Basal LH, IU/l	1.5±1.1	1.6±0.5	0.70
Basal testosterone, ng/ml	1.1±0.6	2.0±1.1	<0.001
Peak LH at GnRH stimulation, IU/l	11.6±4.9	25.5±4.8	<0.001

Values are expressed as means ± standard deviation.

tion study, various confounding factors like the ones mentioned above may have influenced the results of the study, and this is the main limitation of our study.

In this study, it was found that organic CPP cases were diagnosed at a younger age compared to idiopathic cases. Chemaitilly et al. [18] also demonstrated that pubertal findings started earlier in the organic group compared to the idiopathic group. Various studies in boys and girls have shown that the onset of puberty is earlier in organic CPP cases, and given the fact that the possibility of finding an organic cause in cases with an early presentation of pubertal findings is higher, it has been recommended to perform CNS imaging using CT or MRI [19–21] in those who show signs of puberty at very young ages. In the current study, most organic cases had been diagnosed before the age of 7 years, while most of the idiopathic cases had been diagnosed after the age of 7 years. Sixty percent of the cases who had been diagnosed with CPP before the age of 7 years had an underlying organic cause, whereas 92% of the cases who had been diagnosed after the age of 7 years were idiopathic. It is known that girls with CPP who are diagnosed between 6 and 8 years of age are mostly idiopathic, and the odds of detecting an underlying CNS pathology in these girls are very low. Based on the results of our study, it can be suggested that boys with CPP who are diagnosed between 7 and 9 years of age are more likely to be idiopathic, and when making an etiological evaluation, this must be kept in mind. Even though most of the male CPP cases diagnosed after 7 years of age are idiopathic, since there is still a possibility of an underlying organic pathology, CNS imaging should not be abandoned in this age group.

Various studies have shown the association between overnutrition and early puberty [22–26]. The effect of obesity on early puberty has been reported mostly in girls. Different studies investigating the association between body weight and pubertal age in girls have shown that weight gain during childhood was a factor in the earlier onset of puberty [22–24]. On the other hand, there is no consensus on the effect of obesity on pubertal maturation in boys. In contrast to the findings in girls, some studies suggest that obesity is associated with delayed puberty onset in boys [27–29]. However, recent studies have shown that obesity also plays a role in the earlier onset of puberty in boys. An Australian study involving 1,506 boys demonstrated that boys who were overweight at the age of 5 years had advanced pubertal stages when they were 14 years of age [25]. A Swedish study on 2,065 boys demonstrated that cases with higher BMI scores entered puberty earlier [24]. The Copenhagen Puberty Study investigated the effect of increased adiposity on the earlier onset of puberty in boys. Studies between 1991 and 1993 and between 2006 and 2008 have shown that increasing BMI z-scores lead to

an earlier onset of puberty [26]. In the present study, idiopathic CPP cases also had higher BMI-SDS compared to organic cases, indicating that the increase in weight may be a cause for the earlier onset of puberty in boys.

In conclusion, the present study showed that there was no underlying pathological cause in 74% of the male CPP cases, which is quite high, and an organic cause was determined in only 26% of the male patients with CPP. This rate is one of the lowest rates in the literature and indicates that the number of idiopathic male CPP cases is increasing over time. When a boy is diagnosed with CPP above the age of 7 years, the odds of detecting an underlying CNS pathology are very low, and these cases are mostly idiopathic. Similar to girls with CPP, an increase in weight gain during childhood may be a risk factor for the development of precocious puberty in boys. However, further studies are needed to shed light on the relation between adiposity and the onset of puberty in boys.

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