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Original Article

Gender-related differences in etiology of organic central precocious puberty

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ABSTRACT

Background. Central precocious puberty (CPP) is idiopathic in 90% of girls and 60% of boys, while some cases are caused by lesions of central nervous system (CNS), a condition often referred to as organic CPP. We aimed to analyze the etiology of organic CPP in a large cohort of girls and boys and determine gender-related differences.

Methods. Medical files of 256 girls and 120 boys diagnosed and treated for CPP in a single center in the last two decades were reviewed. Patients were classified into four groups with respect to previous history and MRI findings: (1) previously established CNS pathology at the time of diagnosis, (2) novel CNS pathology previously asymptomatic, (3) incidentalomas considered to be unrelated to CPP, and (4) completely normal MRI. Group 1 and 2 were considered as organic CPP whereas group 3 and 4 were considered as idiopathic CPP.

Results. Prevalence of CNS pathology was significantly higher in boys than girls (21.7% vs 6.2%). Previous CNS pathologies such as developmental anomaly of CNS, parenchymal injury, necrotic lesions and hydrocephalus were present in 3.5% of girls and 8.3% of boys. Prevalence of novel CNS pathology as determined by imaging among neurologically asymptomatic patients was 2.8% in girls and 14.5% in boys. The most common novel CNS pathologies in boys were hamartomas (5%) and suprasellar arachnoid cysts (3.3%); which were significantly lower in girls (0.8 and 0.8% respectively). Onset of organic CPP was before six years in girls, and seven years in boys.

Conclusions. Organic CPP was 3.5 times more common in boys compared to girls. It is possible to detect an underlying CNS pathology in one out of every five boys with CPP. Frequency and distribution of organic etiology also differ between girls and boys, hypothalamic hamartomas and suprasellar arachnoid cysts being more common in boys than girls. The likelihood of novel intracranial pathology associated with CPP is quite low in girls with an onset after six years of age and in boys with an onset after seven years of age.

Key words: central precocious puberty, cranial MRI, etiology, pituitary MRI, precocious puberty.

Central precocious puberty (CPP) is idiopathic in up to 90% of girls, and 60% of boys, however, some cases are due to lesions of the central nervous system (CNS), a condition often referred to as organic CPP.[1-5] We have recently shown that majority of CPP in boys were idiopathic rather than organic, however 26% of CPP are still caused by organic lesions of CNS.[6] Nevertheless, boys are more likely to have organic lesions than girls. Hamartomas of the tuber cinereum are the most frequent type of CNS tumor that causes CPP in very young children. Other CNS tumors associated with CPP include astrocytomas, ependymomas, optic and hypothalamic gliomas, and pinealomas. It's yet unclear why organic lesions are more common in boys with CPP. To our knowledge, there is as yet no study comparing the sex distribution of underlying etiology of organic CPP, in order to determine gender-related differences. In this study, we aimed to analyze the etiology of

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organic CPP in a large cohort of girls and boys, and determine gender related differences.

Material and Methods

Medical files of 256 girls and 120 boys diagnosed and treated for CPP in a single center in the last two decades were reviewed. Chronological and bone age, height, pubertal stage, hormone levels as well as findings of CNS imaging at the time of diagnosis were analyzed. Diagnosis of CPP was made in girls clinically by breast development (Tanner stage two or higher) before eight years of age, and biochemically using an elevated serum estradiol (≥ 10 pg/ml), as well as an elevated peak luteinizing hormone (LH) (≥ 5 IU/L) during GnRH test. In boys diagnosis was based on testicular enlargement (≥ 4 ml) before nine years of age with a pubertal elevation of testosterone level (≥30 ng/dl), as well as an elevated peak LH (≥ 5 IU/L) during GnRH stimulation test.[7-9] GnRH test was performed as previously described.[10] Tanner staging was used to determine pubertal stages.[11] Prader orchidometer was used to measure the volume of the testes. All patients except those having organic pathology and those having pubertal stage four or above were followed for three to six months before the treatment decision. GnRHa treatment was given to the cases with progressive CPP which was determined according to the following criteria; a. Growth velocity above six cm/year, b. Advanced bone age (bone age - chronological age ≥ 2 years), c. Rapid progression of pubertal stages (progression of puberty from one stage to another in less than six months), d. Deficit in predicted adult height compared to target height.[12] Those patients with progressive CPP who received GnRHa treatment were included in the study.

Body weight was measured using a digital body weight scale, and height was measured in the standing position with a wall-mounted stadiometer. Bone age was assigned by a pediatric endocrinologist using the method of Greulich and Pyle.[13] The percentile curves of the Centers for Disease Control and Prevention (CDC) were used to interpret the growth data. Height standard deviation scores (SDS) for both chronological and bone age were calculated using CDC charts.

FSH, LH, estradiol (ARCHITECT System, Abbott Laboratory Diagnostics, USA), and testosterone (IMMULITE 2000 System, Siemens, UK) levels were measured using immunochemiluminometric assay (ICMA). Lowest measurable levels of FSH, LH, estradiol and testosterone assays were 0.3 and 0.07 IU/l, 10 pg/ml and 20 ng/dl, respectively.

All patients had an imaging study designed for precocious puberty at 1.5 Tesla MR scanners: axial T2-weighted imaging (WI) (TR/TE; 3000-3800/90-100 ms), diffusion WI (TR/TE; 3500-3800/90-96 ms, applied maximum b value of 1,000 s/mm^2) covering the whole brain in addition to a standard pituitary imaging protocol which included sagittal and coronal T1WI (TR/TE; 530-600/15-20 ms) and coronal T2WI (TR/TE; 3300-3600/85-95 ms), and dynamic T1 coronal and repeat sagittal T1WI imaging following intravenous Gadolinium (Gd)-based contrast material injection.

All MRI studies were evaluated by neuroradiologists for presence of any lesion in the hypothalamic-pituitary region and other CNS lesions located in the brain parenchyma or extraaxial spaces. In cases with an abnormality, a tailored MRI examination was performed where needed. Some of these patients with CNS abnormalities were already being followed-up for their disease when they were studied for precocious puberty and these were recorded. Patients were classified into four groups with respect to previous history and MRI findings: (1) previously established CNS pathology at the time of diagnosis, (2) novel CNS pathology previously asymptomatic, (3) incidentalomas considered to be unrelated to CPP, and (4) completely normal MRI. Group 1 and 2 were considered as organic CPP whereas group 3 and 4 were considered as idiopathic CPP. This study was approved by the Ethics Committee

of Hacettepe University (Approval number: GO 19/452-42). The requirement for informed consent was waived due to the retrospective nature of the study.

Statistical Analyses

Statistical analyses were performed using the Statistical Package for Social Sciences software for Windows (version 19.0; SPSS Inc., Chicago, IL, USA). Continuous variables were reported as the mean ± standard deviation, and categorical variables were shown as numbers and percentage. Student's t-test and one-way ANOVA with post hoc Tukey's HSD test were used to analyze differences between independent groups. Categorical variables were analyzed using Pearson's chi-square, Fisher's exact chi-square or likelihood ratio test. A p value of less than 0.05 was considered statistically significant.

Results

CNS pathology was significantly more prevalent in boys (21.7%) in comparison to girls (6.2%) (p <0.001) (Table I). 3.5% (9/256) of girls and 8.3% (10/120) of boys had previously established CNS pathologies such as developmental anomalies of CNS, parenchymal lesions and hydrocephalus detected by cranial MRIs. All the remaining cases were neurologically asymptomatic. In this group, a novel CNS pathology was identified in 2.8% (7/247) of girls and in 14.5% (16/110) of boys on MRI. The most common novel CNS pathologies in boys were hypothalamic hamartomas (5%) and suprasellar arachnoid cysts (3.3%). The frequency of suprasellar arachnoid cysts (0.8%) and hypothalamic hamartomas (0.8%) were significantly lower in girls (p <0.001) (Table II). Suprasellar arachnoid cysts were > 5 cm in size causing hydrocephalus in all cases. The prevalence of incidentalomas (microadenomas and millimetric pars intermedia cysts) were similar in both sexes (8.6% vs. 9.2%) (Table I).

Puberty started before six years in girls and seven years in boys with CNS pathology. All girls diagnosed with CPP younger than two years as well as boys younger than three years had an underlying hypothalamic hamartoma (Table III). The remaining two boys with hamartomas were diagnosed at four and five years of age. Age at diagnosis was smaller, bone age was greater, height SDS adjusted for bone age was lower, and sex steroid levels and peak LH during GnRH test were higher in patients with a CNS pathology in comparison to those with idiopathic CPP (Table IV).

Discussion

The prevalence of idiopathic CPP in boys is increasing in recent studies, however, organic CPP is still more common in boys than in girls.[6] The prevalence of CNS pathology in CPP, excluding incidentalomas, is 3.3-15.8% in girls, and 26-40% in boys in recent reports.[6,12,14] However, one recent study reported no demonstrable change in the epidemiology of organic CPP in boys.[15] Neurofibromatosis and optic glioma were more common in that study in comparison to ours, while prevalence of hamartomas were similar (6%). Although idiopathic CPP was more common than organic CPP in boys in our study, still, organic CPP was 3.5 times more common in boys compared to

Table I. Cranial and/or pituitary MRI findings of the patients.

	Idiopathic		Organic	
	Normal n (%)	Incidentaloma n (%)	Known CNS pathology* n (%)	Novel CNS pathology** n (%)
Girls	218 (85.2)	22 (8.6)	9 (3.5)	7 (2.7)
Boys	83 (69.2)	11 (9.2)	10 (8.3)	16 (13.3)

* Previously established CNS pathology with neurological symptoms
** Novel CNS pathology without neurological symptoms and signs

Table II. Frequency of CNS pathologies in cases without neurological findings.

	Boys n(%)**	Girls n(%)***	Boys/Girls ratio	p value
Hypothalamic hamartoma	6 (5)	2 (0.8)	6	<0.001
Suprasellar arachnoid cyst	4 (3.3)	2 (0.8)	4	<0.001
Hemorrhagic macroadenoma*	1	2	N/A	N/A
Optic glioma*	2	1	N/A	N/A
Craniopharyngioma*	1	0	N/A	N/A
Pineal germinoma*	1	0	N/A	N/A
Pinealoblastoma*	1	0	N/A	N/A
Total	16(13.3)	7(2.7)	5	<0.001

* Statistical analysis could not be performed due to the small number of cases
** Percent in total number of boys
*** Percent in total number of girls

Table III. CNS findings with respect to age groups as determined by MRI.

	Pituitary or cranial MRI	Age at onset of pubertal findings					
		Girls n=256			Boys n=120		
		0-2 yrs n (%)	2-6 yrs n (%)	6-8 yrs n (%)	0-3 yrs n (%)	3-7 yrs n (%)	7-9 yrs n (%)
Idiopathic CPP	Normal		30 (11.7)	188 (73.4)		12 (10.0)	71 (59.2)
	Incidentaloma		4 (1.6)	18 (7.0)		2 (1.7)	9 (7.5)
Organic CPP	Novel CNS pathology previously asymptomatic	2 (0.8)	5 (2.0)		4 (3.3)	12 (10.0)	
	Previously established CNS pathology (previously symptomatic)		9 (3.5)			10 (8.3)	
Total		2 (0.8)	48 (18.8)	206 (80.4)	4 (3.3)	36 (30)	80 (66.7)

girls (21.7% vs 6.2%). Hypothalamic hamartomas and suprasellar arachnoid cysts were the most common lesions in boys, and hamartomas were six times, arachnoid cysts were four times more frequent in boys than in girls. Interestingly, we did not observe any predominance of a specific lesion in girls. Novel organic CNS lesions in girls included hamartomas, arachnoid cysts, hemorrhagic macroadenoma and glioma, none of which had any predominance over another.

In the literature, lesions associated with CPP are hamartomas, pituitary, pineal or suprasellar arachnoid cysts, hypothalamic pilocytic astrocytomas, pineal tumors or cysts, hypothalamic teratomas, and gliomas.[1,3,16-19] Hypothalamic hamartomas (HH) are rare, tumor-like malformations formed during fetal development. They are present at birth, however, become symptomatic during childhood. Two clinical phenotypes are described. They can either present with CPP or epilepsy and additional neurobehavioral symptoms. For those that present with CPP, symptoms usually start as early as 1-3 years of age, whereas neurological symptoms such as epilepsy present later.[17,19-23] In a study including one boy and 20 girls with CPP, hypothalamic hamartomas were present in 14%, and all showed pubertal signs in the first two years of life.[20] In the current study, pubertal signs were observed before two years of age in two girls with hamartoma, whereas onset of puberty was before three years of age in four boys, and between three and seven years of age in the remaining two. MRI of patients with CPP typically shows HH in the anterior

Table IV. Clinical and hormonal characteristics of patients with organic CPP vs idiopathic.

	Girls			Boys		
	Organic (n=16)	Idiopathic (n=240)	P value	Organic (n:26)	Idiopathic (n=94)	P value
Chronological age at diagnosis (CA) (yrs)	4.6 ± 1.1	7.8 ± 0.8	<0.001	5.0 ± 1.4	8.4 ± 1.1	<0.001
Age at initiation of symptoms (yrs)	4.1 ± 1.1	6.8 ± 0.8	<0.001	4.4 ± 1.4	7.4 ± 0.9	<0.001
Bone age (BA) (yrs)	8.2 ± 0.9	10.0 ± 0.5	<0.001	8.5 ± 1.3	10.2 ± 1.2	<0.001
BA advancement (BA-CA) (yrs)	3.6 ± 1.5	2.2 ± 0.9	<0.001	3.5 ± 0.9	1.8 ± 0.5	<0.001
Height-SDS	1.8 ± 1.0	1.5 ± 0.8	0.355	1.8 ± 1.0	1.1 ± 0.9	<0.001
Height-SDS for BA	-2.3 ± 0.8	-0.7 ± 0.7	<0.001	-1.9 ± 0.9	-0.6 ± 0.7	<0.001
Pubertal stage			0.565			0.456
T2	5 (31.2%)	85 (35.4%)		9 (34.6%)	34 (36.2%)	
T3	9 (56.3%)	125 (52.1%)		13 (50%)	46 (48.9%)	
T4	2 (12.5%)	30 (12.5%)		4 (15.4%)	14 (14.9%)	
Basal FSH (IU/L)	3.8 ± 1.0	4.5 ± 1.5	0.405	3.7 ± 1.4	3.5 ± 1.6	0.505
Basal LH (IU/L)	1.6 ± 0.9	1.3 ± 0.7	0.386	1.5 ± 0.9	1.3 ± 0.9	0.705
Basal E2 (pg/ml)	64.8 ± 21.4	30.6 ± 12.6	<0.001			
Basal testosterone (ng/dl)				94.6 ± 34.0	20.2 ± 13.5	<0.001
Peak stimulated LH (IU/L)	17.1 ± 3.5	12.3 ± 4.1	<0.001	26.2 ± 4.8	13.1 ± 5.0	<0.001

hypothalamus, tuber cinereum and pituitary stalk. For those that present with epilepsy, gelastic (laughing) seizure is usually the first symptom during infancy.

Some brain lesions detected on MRI while investigating the etiology of CPP may indeed be incidentalomas. Incidentaloma, can be defined as a lesion detected through imaging, performed for other reasons rather than to identify an excess or lack of pituitary hormones.[24] In the current study, the prevalence of incidentaloma was similar in both sexes, as well as similar to that reported in the literature.[1,18,25] Suprasellar arachnoid cysts may not always be associated with precocious puberty. Adan et al.[26] reported that only 1/3 of suprasellar arachnoid cysts were associated with precocious puberty. In the current series, all the suprasellar arachnoid cysts were large in size (>5 cm) causing hydrocephalus. Therefore, they were included in the organic group of CPP.

The prevalence of organic lesions is high in early onset CPP. Three recent studies analyzing girls with CPP classified cases with respect to age as younger than 6 years and ≥ 6 years of age. CNS lesions were more prevalent in those with early onset CPP (17.1-26.9%) in comparison to those with later onset CPP (0-1.9%).[3,16,25] In the current study, all cases with an onset before two years of age in girls and three years of age in boys had an underlying organic lesion. None of the girls with an onset of CPP after six years and boys after seven years of age had any organic lesion.

A number of studies analyzed various clinical and biochemical features that may predict intracranial pathology in girls with CPP, however similar studies in boys are scarce. Clinically, the probability of a CNS lesion underlying CPP is higher in girls before five years of age, with rapid pubertal development and significantly advanced bone age.[20,27,28] Studies comparing biochemical features of idiopathic vs organic CPP have conflicting results. In some, higher basal gonadotropin levels, stimulated LH and FSH peaks, as well as basal serum estradiol levels were associated with organic lesions, whereas in others such an association could not be shown.[2,16,17,29-32] In the current study, patients with organic CPP had an earlier onset with advanced bone age, and higher sex steroid levels as well as higher peak stimulated LH.

Magnetic resonance imaging is an expensive, as well as invasive technique requiring intravenous gadolinium injection, and even sedation in some cases. Therefore, it is practical to define criteria to differentiate those with a likelihood of organic lesion in order to use imaging selectively in CPP. There is a common agreement that all boys with CPP should undergo cranial and pituitary MRI. In the current study a novel CNS pathology was detected in 14.5 % of boys, all younger than seven years of age. Likelihood of a novel CNS pathology was five times more frequent in boys compared to girls (14.5% vs 2.8%). Also it is possible to detect a CNS lesion in approximately one out of every five boys with CPP (21.7%). Thus, we also recommend neuroimaging in all boys with CPP.

Since girls are more likely to have idiopathic CPP, there are conflicting opinions on CNS imaging in girls especially in those aged 6-8 years. There are studies that suggest routine brain and pituitary MRI should not be carried out on girls who are neurologically normal and whose puberty started after six years of age since likelihood of underlying intracranial pathology and tumor in girls at this age group is quite low.[25,33] However, other studies recommend MRI in all girls with CPP regardless of age in order to rule out an underlying CNS lesion even if the risk is low.[1,27,30] Based on our data, we recommend a cranial and pituitary imaging to all girls younger than six years of age. We believe that routine MRI is unnecessary beyond six years of age in girls unless there are neurological findings.

Organic CPP is 3.5 times more common in boys compared to girls. It is possible to detect an underlying CNS pathology in one out of every five boys with CPP. Frequency and distribution of organic etiology also differ between girls and boys. In boys, organic causes are more frequent, and hypothalamic hamartomas and suprasellar arachnoid cysts are more common than girls. Organic cause underlying CPP is quite rare in girls older than six years, and boys older than seven years. We recommend pituitary and cranial MRI for all boys with CPP regardless of age since there is a risk of CNS lesion in one out of every five boys with CPP. The likelihood of novel intracranial pathology associated with CPP is quite small in girls with an onset after six years of age. We recommend pituitary and cranial MRI for all girls with a pubertal onset younger than six years, as well as those with accompanying neurological findings suggestive of intracranial lesion in those with an onset of puberty after six years of age.

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