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Clinical Research Article

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Cranial MRI Abnormalities and Long-term Follow-up of the Lesions in 770 Girls With Central Precocious Puberty

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Abbreviations: BMI, body mass index; CNS, central nervous system; CPP, central precocious puberty; LH, luteinizing hormone; FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; MRI, magnetic resonance imaging; OR, odds ratio; SDS, standard deviation score.

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Abstract

Context: Central precocious puberty (CPP) may arise from central nervous system (CNS) lesions in a few affected girls. Recently, the incidence of girls with CPP has increased mostly in 6-8 year olds, in whom the necessity of magnetic resonance imaging (MRI) is debated.

Objective: To investigate the frequency, long-term outcome and potential predictors of CNS lesions in a large cohort of girls with CPP.

Methods: A multicenter cohort of 770 Turkish girls with CPP who had systematic cranial MRI between 2005 and 2017. Age at puberty onset was <6 years in 116 and 6-8 years in

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654. CNS lesions were followed until final decision(6.2 ± 3.1 years). Potential predictors of CNS lesions were evaluated by univariate analyses.
Results: A total of 104/770 (13.5%) girls had abnormal brain MRI. Of these, 2.8% were previously known CNS lesions, 3.8% had newly detected and causally related CNS lesions, 3.1 % were possibly, related and 3.8% were incidental. Only 2 (0.25%) neoplastic lesions (1 low grade glioma and 1 meningioma) were identified; neither required intervention over follow-up of 6 and 3.5 years respectively. Age at breast development <6 years (odds ratio [OR] 2.38; 95% CI 1.08-5.21) and the peak luteinizing hormone/follicle-stimulating hormone (LH/FSH) ratio >0.6 (OR 3.13; 95% CI 1.02-9.68) were significantly associated with CNS lesions. However, both patients with neoplastic lesions were >6 years old.
Conclusion: Although age and LH/FSH ratio are significant predictors of CNS lesions, their predictive power is weak. Thus, systematic MRI seems to be the most efficient current approach to avoid missing an occult CNS lesion in girls with CPP, despite the low likelihood of finding a lesion requiring intervention.

Key Words: Precocious puberty, magnetic resonance imaging, CNS imaging, MRI, organic

Central precocious puberty (CPP) in girls is defined by progressive sexual maturation stemming from hypothalamic–pituitary–gonadal activation with ensuing sex hormone secretion, before 8 years of age. About 90% of girls with CPP present with the idiopathic form, whereas a varying proportion (0-27%) of girls with CPP are reported to have central nervous system (CNS) abnormalities/lesions, including hydrocephalus, cysts, trauma, inflammatory disease, neoplasia, and developmental abnormalities (1-11). Magnetic resonance imaging (MRI) of the brain is, therefore, recommended to rule out CNS abnormalities/lesions in patients with CPP. However, controversy exists regarding the age limits for routinely performing MRI in girls diagnosed with CPP, since the likelihood of finding CNS abnormalities decreases with increasing age (4-6, 10). A consensus paper on CPP, written by the experts in the field in 2007, stated that "It is controversial whether all girls who develop CPP between 6 and 8 years of age require head MRI. Girls with neurologic findings and rapid pubertal progression are more likely to have intracranial pathology and require an MRI examination" (12). Nevertheless, there are studies supporting (4, 5) or challenging (9) that statement and there is no uniform practice among clinicians regarding requirement of MRI in girls with CPP above 6 years of age.

It is true that a small number of girls with CPP but no other neurological symptoms might have serious CNS lesions, such as a tumor and other progressive pathologies, which require intervention. However, most abnormalities reported on MRI are either incidental and not causally related with CPP or abnormalities that do not require any intervention (1-11). There is potential harm due to administration of contrast agents as well as intravenous sedation associated with MRI. Additionally, anxiety in children, and in their parents, and the possibility of finding an incidental lesion, which is not related to CPP but requires repeated MRI and follow-up visits, as well as healthcare cost needs to be considered. Furthermore, there is an ongoing trend towards increased and, perhaps, overdiagnosis of CPP in girls aged 6-8 years worldwide over the past 20 years (13, 14). Thus, the classical concept of CNS imaging in all girls with CPP has been challenged and the question of "which girls with CPP should have a CNS imaging?" is currently a matter of debate. Furthermore, long-term data are scarce regarding the outcome of the lesions detected on brain MRI in girls with CPP in the previous studies (1-8, 11). The aim of this retrospective, multicenter study is to evaluate the frequency of CNS abnormalities and the outcome of these abnormalities after long-term follow-up in a large cohort of girls with CPP and to evaluate possible predictive factors in girls with CNS lesions without neurologic findings.

Patients and Methods

This retrospective, multicenter study used a common case recording form to collect the demographic, clinical, and laboratory data, brain MRI results, and the follow-up of those with abnormal brain MRI, in girls who were diagnosed with CPP between July 2005 and July 2017. In all participating centers, brain MRI was routinely performed in all girls with CPP before the initiation of gonadotropin releasing hormone (GnRH) treatment, regardless of age. All MRIs were performed before and after gadolinium-enhanced T1- and T2-weighted images in axial, coronal, and sagittal sections. The criteria for the diagnosis of CPP were (1) progressive breast development starting <8 years of age associated with accelerated growth and skeletal

maturation; and (2) a peak luteinizing hormone (LH) of at least 5 IU/L (12, 15-20) on GnRH stimulation test (19). Furthermore, girls with basal LH levels above 0.3 IU/L, who also met the above criteria, were assumed to have CPP if no GnRH stimulation test was performed (16, 21). All girls also had pelvic ultrasound evaluation. Uterine length >34 mm and ovarian volume >2 cubic centimeters (cc) were taken as supportive criteria (12, 22, 23).

Pubertal development was staged according to the Marshall and Tanner criteria (24). Height and weight were measured, body mass index (BMI) was calculated using the standard formula [weight in kg/(height in m)^2], and the respective standard deviation score (SDS) were calculated based on local reference data (25-27). Bone age was assessed by X-ray of the left hand, according to the method of Greulich and Pyle (28). Fasting venous blood samples were obtained from all girls in the morning for follicle-stimulating hormone (FSH), LH, and estradiol measurements. All centers were using semi-automated chemiluminescence methods for hormonal measurements.

The MRI findings were categorized as (1) normal MRI or (2) abnormal MRI. Abnormal MRIs were further subgrouped into (1) previously known CNS lesion at the time of diagnosis of CPP or (2) newly identified CNS lesion on MRI without neurological symptoms. The latter subgroup was further categorized into (1) MRI findings causally related to CPP; (2) questionably related to CPP; or (3) incidental findings. Arachnoid cysts, hypothalamic hamartomas, hydrocephalus, solitary lesions, subependymal nodules, encephalocele, encephalomalacia, and neural tube defects were considered as causally related to CPP. Rathke cleft/pars intermedia cysts, gliosis, and mega cisterna magna were considered to be questionably related, whereas pituitary microadenomas, pineal cysts, vascular abnormalities, and other common structural abnormalities were considered as incidental findings, based on the general consensus in the literature (9, 11, 29).

The study protocol was approved by the Marmara University Ethics Committee (approval number: 092020737) and was conducted in accordance with Helsinki Declaration.

Statistical Analyses

The statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software, version 17.0 (IBM Inc., Chicago, IL, USA). Diagnostic groups were compared using independent t-test, Mann–Whitney U test, and chi-squared tests where appropriate. Probability value of $P < .05$ was considered statistically significant. For determination of the predictors of new and clinically significant CNS lesions, a new group (n = 29) was formed which consisted of 28 patients with new CNS lesions causally related to CPP and potentially requiring intervention (13 arachnoid cysts, 8 new hamartomas, 4 new hydrocephalies, 1 tuberous sclerosis, 1 glial tumor, 1 meningioma) and 1 patient with a pars intermedia cyst who required surgery in the follow-up. Potential predictors of new and clinically significant brain abnormalities were dichotomized. Univariate analysis was performed using the 2-tailed Fisher exact test to evaluate the association between potential predictors and the detection of CNS lesions. Odds ratio (OR) and 95% CI sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and likelihood ratios were calculated for each potential predictors in this group compared to the MRI normal group. For comparison of estradiol levels, in addition to concentrations, the 45th percentile was determined according to the distribution within each center to take into consideration the probable variability of estradiol measurement techniques among centers.

Results

A total of 785 cases from 9 participating centers were initially considered. The adequacy of the diagnoses was reviewed by 2 of the authors (D.H.; A.B.) for consistency and accuracy. Out of the 785 girls; 15 were excluded because of the age of onset of breast development >8.0 years of age in 10 and failure to meet laboratory criteria in the other 5. The remaining 770 patients were included in the final analyses. In these 770 girls, 666 (86.5%) had normal MRI (Table 1) and the remaining 104 (13.5%) patients had CNS abnormalities on MRI. Within each group, the number of girls who did not have a GnRH stimulation test because of elevated baseline LH were MRI normal group (n = 20; 3%); MRI abnormal group (n = 16; 15.4%). In the abnormal MRI group; 22/104 (21%) CNS abnormalities had been noted prior to the diagnosis of CPP due to neurological symptoms, constituting 2.85% of all patients. These were neural tube defects (n = 8) including spina bifida/myelomeningocele/Chiari II malformation), hydrocephalus (n = 6), West syndrome, and operation for refractory epilepsy and postoperative encephalomalacia (n = 1); epilepsy and cystic encephalomalacia (n = 1), epilepsy in whom MRI revealed hypothalamic hamartoma (n = 1), cerebral palsy and encephalocele (n = 1), cerebral palsy, leukomalacia and corpus callosum hypoplasia (n = 1), global developmental delay in whom MRI showed hypothalamic hamartoma (n = 1), cerebral palsy, epilepsy and hydrocephaly (n = 1), and neurofibromatosis and optic glioma (n = 1). The remaining 82 abnormalities were newly discovered on MRI performed exclusively for CPP (82/770 = 10.6 % of all CPP girls). The most common findings were pituitary microadenoma-like lesions, which were proven to be incidentalomas upon follow-up (n = 18). The others were arachnoid cysts (n =

Table 1. Description of 104 brain MRI scans with abnormal findings with their percentage (in parenthesis) among the age groups <6 years and >6 years at the time of puberty onset in girls with CPP

All (n = 770)	Normal MRI (n = 666)	Abnormal MRI (n = 104)		
<6 years, 116	<6 years, 88 (75.9%)	<6 years, 28 (24.1%)		
>6 years, 654	>6 years, 578 (88.4%)	>6 years, 76 (11.6%)		
		Known MRI abnormalities at diagnosis of CPP (n = 22)	**Newly diagnosed MRI abnormalities (n = 82)**	
		<6 years, 9/116 (7.7%) >6 years, 13/654 (2.0%)	<6 years, 19/116 (16.4%) >6 years, 63/654 (9.6%)	
			Causally related (n = 29)	**Questionably related (n = 24)**	**Incidental finding (n = 29)**
			<6 years, 8/116 (6.9%) >6 years 21/654 (3.2%)	<6 years 7/116 (6.0%) >6 years 17/654 (2.6%)	<6 years 4/116 (3.5%) >6 years 25/654 (3.8%)
		Neural tube defects (n = 8)	Arachnoid cyst (n = 13)	Rathke cleft/Pars intermedia cyst (n = 11)	Pituitary microadenoma (n = 18)
		Hydrocephalus (n = 6)	Hypothalamic hamartoma (n = 8)	Gliosis (n = 6)	Pineal cyst (n = 7)
		West syndrome, operation for refractory epilepsy, postoperative cystic encephalomalacia (n = 1)	Hydrocephalus (n = 4)	Mega cisterna magna (n = 5)	Pituitary macroadenoma (n = 1)
		Epilepsy and cystic encephalomalacia n = 1)	Tuberous sclerosis (n = 1)	Partial empty sella (n = 1)	Basal ganglia hyperintensities (n = 1)
		Epilepsy, hypothalamic hamartoma and cortical heterotopia of occipital lobe (n = 1)	Low grade glial tumor (n = 1)	Cavum septum pellucidum (n = 1)	Arteriovenous fistula (n = 1)
		Cerebral palsy and encephalocele (n = 1)	Meningioma(n = 1)		Developmental venous anomaly (n = 1)
		Cerebral palsy, leukomalacia and corpus callosum hypoplasia (n = 1)	Encephalomalacia (n = 1)		
		Neurodevelopmental delay with hypothalamic hamartoma (n = 1)			
		Neurodevelopmental delay, epilepsy, cerebral palsy, hydrocephaly (n = 1)			
		Neurofibromatosis and optic glioma (n = 1)			

13), Rathke cleft/pars intermedia cysts (n = 11), hypothalamic hamartomas (n = 8), pineal cysts (n = 7), gliosis (n = 6), hydrocephalus (n = 4), mega cisterna magna (n = 5), low-grade glial tumor (n = 1), meningioma (n = 1), arteriovenous fistula (n = 1), developmental venous anomaly (n = 1), encephalomalacia (n = 1), partial empty sella (n = 1), cavum septum pellucidum abnormality (n = 1), pituitary nonfunctioning macroadenoma (n = 1), subependymal nodules due to tuberous sclerosis (n = 1), and basal ganglia hyperintensities of unknown etiology (n = 1) (Table 1). All

girls with MRI lesions were evaluated by specialists in the neurology or neurosurgery sections, and all of them were followed after GnRH analogue discontinuation until resolution or clinical definition of the CNS lesion surveillance. The mean duration of follow-up in those with MRI lesions was 6.2 ± 3.1 years.

In 18 girls, contrast-enhancing heterogeneities, ranging in size between 2 and 4 mm; within the pituitary gland were reported as pituitary microadenomas. These girls did not have any other clinical or pituitary hormonal abnormality other than CPP. Repeat MRIs were performed in 11 (61.1%) of them. The lesion disappeared in 4, reduced in size in 1 and remained the same size in 6 of the girls after an average duration of follow-up of 6.5 ± 3.2 years, hence all of them were considered incidental. One girl had pituitary macroadenoma (12 mm) but did not have any symptoms, hormonal abnormalities or an increase in adenoma size during follow-up over 6.5 years.

Children with hypothalamic hamartoma (n = 10, 8 new, 2 known) presented much younger than the rest of the cohort with a mean age of 4.23 ± 3.28 vs 7.65 ± 1.40 years (P = .0009). However, they presented with more advanced Tanner stage (90% of girls with hamartoma had Tanner stage ≥3 vs 61% in the rest of the cohort, P < .001) and higher median (interquartile range) estradiol of 35.1 (21.0-55.6) vs 17.85 (7.5-30.7) pg/mL (P = .015), basal LH 2.55 (1.16-3.90) vs 0.63 (0.18-1.89) IU/L (P = .006) and stimulated LH 17.0 (8.0-41.1) vs 7.87 (5.0-13.2) IU/L (P = .04) concentrations.

In 4 patients, initial MRIs were interpreted as having newly detected, solitary (mass) lesions. However, on long-term follow-up, only 2 of them were proven to be neoplastic; 1 patient had a biopsy-proven, low-grade glioma in the thalamus, and another had a frontal meningioma. Thus, in the group as a whole, only 2/770 (0.26%) patients had a new neoplastic lesion; although none required intervention during close follow-up by both oncology and neurosurgery departments. The clinical characteristics of the 4 patients with solitary lesions are detailed below.

In a 7.4-year-old girl initial MRI reported a 12 mm solitary lesion in the brain stem, which could indicate a tumoral, demyelinating, or postinfectious lesion. After neurosurgery consultation, a decision was made to follow-up with serial MRIs and, after 8 years of uneventful clinical and MRI follow-up, it was decided that this area was most likely a gliosis.

In a 7-year-old girl the initial MRI showed a 15 × 12 mm contrast-enhancing lesion in the left inferior frontal gyrus, which was interpreted as a meningioma. A 4-mm Rathke cleft cyst was also noted. After neurosurgery consultation, it was decided to follow her with repeat MRIs. After 3.5 years of follow-up, the meningioma size remained stable and she had no neurological symptoms. Her basal LH (2.2 IU/L) and estradiol (50 pg/mL) were markedly elevated and uterine length (62 mm) was increased; with an advanced bone age of between 10 and 11 years.

In a 2.7-year-old girl initial MRI demonstrated a 15 × 14 × 12 mm suprasellar hypothalamic tumor located between the mamillary body and the pituitary infundibulum, suggesting a low-grade glioma. An 8 mm pineal cyst was also noted. After 2 years of oncology and neurosurgery follow-up there was no increase in the size of the hypothalamic tumor. In the most recent MRI, the lesion was interpreted as tuber cinereum hamartoma, not requiring intervention. She had Tanner stage III breast development, and markedly elevated basal LH (3.8 IU/L) and estradiol (37.4 pg/mL) and advanced bone age (6.8 years).

In the fourth girl with breast development around 8 years of age, diagnosis of CPP was made at the age of 8.6 years and MRI showed a left thalamic tumor of 28 × 20 mm in dimension extending to the mesencephalon. An 11 × 6 mm Rathke cleft cyst was also noted. A biopsy and immunohistochemistry of the thalamic tumor was consistent with a low-grade glial tumor, a pilocytic astrocytoma. During 6 years of follow-up in oncology and neurosurgery, no increase in the lesion size was identified; thus, no intervention was required. This patient`s hypothalamo–pituitary–gonadal activation was also very robust, as evidenced by markedly elevated basal LH (2.73 IU/L) and estradiol (32 pg/mL), with breast staging of Tanner IV. Her bone age was 11 years.

In the group of 104 MRI abnormalities as a whole, only 5 (4.8%) patients required intervention. One Rathke cleft cyst was operated on due to growth in size and compression of the pituitary gland. Four patients with hamartoma were operated due to refractory seizures. Thus, among girls with CPP, 5/770 (0.6%) patients presented with CNS pathologies that required surgical intervention. However, only 1 of them (Rathke cleft cyst) was above 6 years of age at the time of detection of her CNS lesion. Furthermore, in all 4 hamartoma patients, the reason for operation was refractory epilepsy.

Comparison of the Girls With Normal and Abnormal MRI

Comparison of the MRI normal group with the MRI abnormal group demonstrated that breast development was significantly earlier in the latter (7.04 ± 1.37 vs 6.31 ± 2.11 years; P < .001) and there were significantly more subjects aged <6 years in the MRI abnormal group (13.2 vs

26.9%; respectively, $P < .001$). Patients with known MRI abnormality were significantly younger and had lower height SDS than other groups. The ratio of bone age to chronological age did not differ among the groups. Among the other clinical parameters only peak LH and peak LH/FSH was significantly higher in MRI abnormal groups; median (interquartile range) 10.1 (6.38-17.0) vs 7.6 (4.9-12.8) IU/L, $P < .01$; and 0.90 (0.55-1.28) vs 0.64 (0.35-1.04), $P < .01$; respectively. There were no differences between MRI abnormal and MRI normal groups in regard to the other parameters studied (Table 2).

Clinical and Biochemical Predictors of a Pathological MRI

Significant associations with CNS abnormalities were age at breast development before 6 years with OR (95% CI) of 2.38 (1.08-5.21) and the peak stimulated LH/FSH ratio >0.6 (OR 3.13; 95% CI 1.02-9.68) (Table 3). Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and likelihood ratios calculated for each potential predictor are shown in Table 4.

Discussion

In this multicenter cohort of 770 girls with CPP and cranial MRI imaging, 13.5% had a CNS abnormality. Furthermore, after excluding those with previously known CNS lesions and those with incidental and questionably related lesions, only 3.8% of the girls with CPP and no other CNS symptoms had newly detected and causally related CNS lesions. Most importantly, only 2 (0.25%) neoplastic lesions, 1 a low-grade glioma and the other a meningioma, were identified, neither of which required intervention over 6 and 3.5 years of follow-up, respectively. Age at breast development <6 years of age and stimulated LH/FSH ratio >0.6 appeared as significant predictors of a CNS lesion in the present cohort.

The strength of our study was that we were able to collect information on the long-term outcome of the CNS lesions detected by MRI in regard to the prognosis and requirement for intervention. It was reassuring to observe that even in the 2 neoplastic cases no intervention was required. The other important aspects of the present study are being the largest group of patients studied to date and systematic MRI in all girls diagnosed with CPP. The weaknesses of the study are its retrospective nature and the difficulties due to the multicenter approach.

The prevalence of CNS lesions among the girls with CPP in the present study is comparable to earlier studies, despite a marked recent increase in the prevalence of CPP among girls observed worldwide. This recent increase has mostly been observed among the 6-8 years group, the age group that is known to have less MRI pathology (14, 30, 31). In a multicenter Italian study performed between 1988-1998, 56/304 (18.4%) CPP girls had MRI abnormalities and of these 30 (9.9%) were due to previously diagnosed intracranial abnormalities and the remaining 26 (8.5%) were detected at the time of diagnosis of CPP (4). The frequency of CNS lesions tended to be higher in girls under 4 years of age while the frequency of idiopathic CPP tended to be higher in girls aged between 7 and 7.9 years, without statistically significant differences. In that study, a total of 6 tumoral cases were detected in the whole group, 2 of which were in girls above 7 years of age (1 pinealoma and 1 tumor of the fourth ventricle). No follow-up information regarding the requirement of intervention and the prognosis of the patients was provided.

Another study of 182 girls with CPP covering the period 1990-2012 demonstrated only 3% of CNS lesions, all of them being hamartomas (10). 54 repeat MRIs were performed in 28 CPP girls with incidental CNS lesions with a maximum follow-up of 9 years, and no enlargement of the lesions was seen. Girls with hamartomas were younger than 6 years and had significantly higher mean baseline and stimulated LH values, LH-to-FSH ratio, serum 17β-estradiol levels, and uterine length. However, all the parameters overlapped extensively in girls with or without CNS lesions. Pedicelli et al. concluded that the data cast doubt on the need for routine screening by cranial MRI in girls with idiopathic CPP older than 6 years (10). Hamartoma cases in our cohort shared similar characteristics with the cases in that study and were significantly younger, had more advanced Tanner stage, and had higher estradiol and LH concentrations.

In France, 11 (6%) of 197 girls with CPP had a detected CNS lesion, including 6 hamartomas and 3 gliomas (5). Two girls (1 glioma and 1 hamartoma) were above 7 years of age. The same group did a follow-up, multicenter, European study evaluating 443 girls with CPP diagnosed over the period 1985-2002 and found overall CNS abnormalities in 8% of the study population, although this proportion varied among centers from 3% to 18% (6). The most common finding was again hamartoma (n = 23), but 7 girls with astrocytoma were also diagnosed. Three astrocytoma and 2 hamartoma patients were older than 6 years of age. They concluded that systematic CNS imaging should be performed in all CPP girls but in settings where this is not possible, 2 criteria (age >6 years and estradiol level <45th percentile) could safely help to avoid more than one third of unnecessary cranial imaging.

In the multicenter European study (6); 9% of the girls, and in the Italian multicenter study (4) as many as 30%

Table 2. Comparison of demographic, clinical, biochemical and radiological characteristics of girls with CPP according to brain MRI findings

	All (n = 770)	MRI normal (n = 666)	MRI abnormal—all (n = 104)	MRI Abnormal already known (n = 22)	MRI Abnormal newly diagnosed (n = 82)	MRI abnormal new and causally related (n = 29)	P1	P2	P3	P4
Age at breast development[a]	6.94 ± 1.51	7.04 ± 1.37	6.31 ± 2.11	5.81 ± 2.21	6.45 ± 2.08	6.67 ± 1.65	**0.0001**	**0.0001**	**0.001**	0.163
Age[+] <6 years	116 15.07%	88 13.21%	28 26.92 %	9 40.91%	19 23.17%	8 27.58%	**0.0001**	**0.0001**	**0.015**	**0.027**
>6 years	654 84.93%	578 86.79%	76 73.07 %	13 59.09%	63 76.83%	21 72.41%				
Age at pubic hair	7.49 ± 1.35	7.53 ± 1.21	7.27 ± 1.98	6.8 ± 2.01	7.35 ± 1.99	6.88 ± 2.41	0.187	0.1	0.381	0.059
Maternal age of menarche	12.45 ± 1.35	12.42 ± 1.32	12.65 ± 1.58	12.78 ± 1.48	12.63 ± 1.6	13.18 ± 1.53	0.182	0.426	0.246	**0.013**
Age at treatment (years)[a]	7.9 ± 1.31	7.98 ± 1.19	7.4 ± 1.81	7.05 ± 1.82	7.5 ± 1.8	7.61 ± 1.51	**0.0001**	**0.001**	**0.002**	0.122
Height SDS[b] at treatment	1.08 ± 1.18	1.07 ± 1.18	1.1 ± 1.17	0.15 ± 1.34	1.31 ± 1.03	1.20 ± 0.1.28	0.541	**0.006**	0.057	0.498
Weight SDS[b] at treatment	1.11 ± 1.06	1.12 ± 1.02	1.02 ± 1.27	0.51 ± 1.6	1.16 ± 1.15	1.16 ± 1.39	0.747	0.076	0.622	0.675
BMI SDS[b] at treatment	0.79 ± 0.95	0.81 ± 0.91	0.65 ± 1.17	0.57 ± 1.35	0.67 ± 1.13	0.70 ± 1.35	0.294	0.543	0.37	0.965
BA/CA[b]	1.29 ± 0.31	1.29 ± 0.3	1.31 ± 0.36	1.31 ± 0.38	1.31 ± 0.36	1.30 ± 0.21	0.748	0.8	0.81	0.295
Uterus length (mm)	35.96 ± 10.77	35.83 ± 10.54	36.82 ± 12.14	34.64 ± 13.76	37.42 ± 11.69	40.37 ± 14.51	0.716	0.357	0.38	0.179
Uterus volume (mm^3)[b]	5.43 ± 5.35	5.41 ± 5.2	5.53 ± 6.26	5.14 ± 6.72	5.64 ± 6.17	7.79 ± 9.14	0.663	0.142	0.815	0.184
Right ovary volume (mm^3)[b]	2.33 ± 1.74	2.33 ± 1.72	2.33 ± 1.89	1.81 ± 1.53	2.47 ± 1.97	3.04 ± 2.25	0.722	0.147	0.744	0.056
Left ovary volume (mm^3)[b]	2;24 ± 1;67	2;22 ± 1;66	2;36 ± 1;77	1;76 ± 1;35	2;52 ± 1;84	3;07 ± 2;07	0;421	0;288	0;154	0;165
E2 (pg/mL)[b]	23.34 ± 22.69	23.08 ± 22.32	25.1 ± 25.07	28.76 ± 30.1	24.01 ± 23.5	28.53 ± 28.15	0.451	0.294	0.749	0.227
Basal LH (IU/L)[b]	1.43 ± 2.01	1.39 ± 1.95	1.7 ± 2.37	2.35 ± 3.15	1.53 ± 2.11	1.63 ± 1.64	0.107	0.125	0.281	0.265
Peak LH (IU/L)[b]	11.48 ± 12.12	10.87 ± 10.89	15.29 ± 17.61	22.8 ± 31.11	13.11 ± 10.56	15.05 ± 11.59	**0.002**	**0.012**	**0.025**	0.064
Basal FSH (IU/L)[b]	3.84 ± 2.4	3.83 ± 2.43	3.96 ± 2.19	4.84 ± 2.9	3.71 ± 1.91	4.11 ± 1.87	0.275	0.065	0.75	0.197
Peak FSH (IU/L)[b]	13.79 ± 5.61	13.73 ± 5.73	14.16 ± 4.77	15.26 ± 5.85	13.83 ± 4.41	15.04 ± 5.95	0.265	0.261	0.484	0.338
Peak LH/FSH ratio[b]	0.88 ± 0.84	0.84 ± 0.74	1.13 ± 1.27	1.73 ± 2.38	0.95 ± 0.6	1.01 ± 0.58	**0.004**	**0.032**	**0.026**	0.071

The values in bold represent $P < .05$.

p: MRI normal group versus p1: MRI abnormal p2: MRI abnormal already known p3: MRI abnormal newly diagnosed p4: MRI abnormal new and causally related.

Abbreviations: BA, bone age; CA, chronological age; BMI, body mass index; SDS, standard deviation score; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone.

[a]Independent t test.

[b]Mann–Whitney U test + chi-squared test.

Table 3. Relationship between potential clinical predictors of newly diagnosed and clinically significant CNS abnormalities in girls with CPP[a]

		Newly diagnosed and clinically significant MRI lesion (n = 29)	Normal MRI (n = 666)	OR (%95 CI)	*P*
Age at breast development	<6 years	27.59%	13.21%	2.38 (1.08-5.21)	**.027**
	>6 years	72.41%	86.79%		
Height SDS at treatment	≥0.75	62.07%	60.06%	1.08 (0.51-2.34)	.829
	<0.75	37.93%	39.94%		
Weight SDS at treatment	≥0.75	68.97%	62.31%	1.34 (0.60-2.99)	.469
	<0.75	31.03%	37.69%		
BMI SDS at treatment	≥0.60	58.62%	60.51%	0.92 (0.43-1.96)	.839
	<0.60	41.38%	39.49%		
BA/CA	≥1.1	82.14%	86.13%	0.74 (0.27-1.99)	.552
	<1.1	17.86%	13.87%		
E2 (pg/mL)	>25 pg/mL	37.50%	31.65%	0.77 (0.33-1.79)	.546
	≤25 pg/mL	62.50%	68.35%		
E2 percentile	≥45 Per.	56.00%	47.24%	1.42 (0.64-3.18)	.390
	<45 Per.	44.00%	52.76%		
Uterus length (mm)	≥35	58.33%	57.24%	1.04 (0.46-2.39)	.915
	<35	41.67%	42.76%		
Uterus volume (cc)	≥3.5	60.87%	53.82%	1.33 (0.56-3.14)	.506
	<3.5	39.13%	46.18%		
R+L ovary volume (cc)	≥4	20.83%	17.43%	1.24 (0.45-3.41)	.668
	<4	79.17%	82.57%		
Basal LH mIU/mL	≥1	53.57%	41.00%	1.66 (0.77-3.54)	.186
	<1	46.43%	59.00%		
Basal FSH mIU/mL	≥3	67.86%	53.36%	1.85 (0.82-4.14)	.132
	<3	32.14%	46.64%		
Peak FSH mIU/mL	≥20	22.22%	11.06%	2.30 (0.73-7.26)	.146
	<20	77.78%	88.94%		
Peak LH mIU/mL	≥10	44.44%	36.94%	1.36 (0.53-3.53)	.518
	<10	55.56%	63.06%		
Peak LH/FSH ratio	≥0.66	77.78%	52.73%	3.13 (1.02-9.68)	**.037**
	<0.66	22.22%	47.27%		

The values in bold represent $P < .05$.

Abbreviations: BA, bone age; CA, chronological age; BMI, body mass index; SDS, standard deviation score; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; (R+L), right+left.

[a]Newly diagnosed and clinically significant CNS abnormalities were lesions considered with potential to require intervention.

of girls did not undergo cranial imaging. In contrast, we systematically performed MRI on all girls with CPP, which could be 1 of the reasons for the lower prevalence of tumoral etiologies and higher prevalence of non-tumoral MRI abnormalities in our study.

In the present study, in addition to 8 new hamartoma cases, there were 4 cases with solitary lesions on MRI. However, in long-term surveillance, only 2 (0.25%) were diagnosed as neoplasia. Furthermore, neither of the 2 neoplastic lesions in our cohort required intervention during several years of follow-up; since serial MRIs did not show any progression. Interestingly, 3 patients with new hamartomas (8 years, 8.08 years, and 7.5 years) and the patients with glial tumor (8.6 years) and meningioma (7 years) were older than 6 years of age in our cohort. Thus, despite the finding that age <6 years appeared to be a risk factor for MRI abnormalities in our cohort, in keeping with reports of earlier cohorts, there were cases above 6 years of age who still had clinically significant MRI abnormalities, although these lesions did not necessarily require intervention. Mogensen et al. (9) in 2012, reported 229 girls with CPP, 54 (23.6%) having cranial MRI abnormalities, 21 (9.2%) of them were previously known, and 20 (8.7%) having incidental findings. Only 13 (5.7%) had a pathological cranial MRI including 3 CNS tumors. After repeat MRIs in 10 (out of 13),only 1 girl (a 6.5 year old) with pilocytic astrocytoma needed surgery. Twelve (out of 20) girls with incidental findings had 2 or more MRI scans during follow-up. None of them needed surgery. The authors concluded that all girls with CPP should continue to be examined by cranial MRI since a high frequency of 6- to 8-year-old

Table 4. Sensitivity; specificity; positive predictive value; negative predictive value; accuracy and likelihood ratio of clinical predictors of newly diagnosed and clinically significant CNS abnormalities in girls with CPP

	Sensitivity	Specificity	PPV	NPV	Accuracy	LR (+)
Age at breast development	0.28	0.87	0.16	0.96	0.84	2.08
Height SDS at treatment	0.62	0.40	0.04	0.96	0.41	1.03
Weight SDS at treatment	0.69	0.38	0.05	0.97	0.39	1.11
BMI SDS at treatment	0.59	0.39	0.04	0.96	0.40	0.97
BA/CA	0.82	0.14	0.04	0.95	0.17	0.95
E2 (pg/mL)	0.63	0.32	0.03	0.96	0.33	0.91
E2 Percentile	0.56	0.53	0.04	0.97	0.53	1.19
Uterus length (mm)	0.58	0.43	0.04	0.96	0.43	1.02
Uterus volume (mm^3)	0.61	0.46	0.05	0.97	0.47	1.13
Total (R+L) ovary volume (mm^3)	0.21	0.83	0.05	0.96	0.80	1.20
Basal LH mIU/mL	0.54	0.59	0.05	0.97	0.59	1.31
Basal FSH mIU/mL	0.68	0.47	0.05	0.97	0.48	1.27
Peak FSH mIU/mL	0.22	0.89	0.08	0.97	0.86	2.01
Peak LH mIU/mL	0.44	0.63	0.05	0.97	0.62	1.20
Peak LH/FSH ratio	0.78	0.47	0.06	0.98	0.48	1.48

Abbreviations: PPV, positive predictive value; NPV, negative predictive value; LR (+), positive likelihood ratio; BA, bone age; CA, chronological age; BMI, body mass index; SDS, standard deviation score; E2, estradiol; FSH, follicle-stimulating hormone; LH, luteinizing hormone; (R+L), right+left.

girls with precocious puberty had a pathological cranial MRI, which, unlike in the Chalumeau et al. (6) study, could not be predicted from any clinical or biochemical parameters.

A recent Taiwanese study examined 251 cranial MRIs in girls with CPP reported lesions in 61 (24.3%) of the patients (32). However, only 1 (0.4%) patient with hypothalamic hamartoma who was aged below 6 years was found to be related to CPP. 45 of the patients with CNS lesions underwent repeat MRIs and none showed progression; and 20% showed regression of the lesions similar to that observed in our study.

Evaluation of potential clinical predictors of an abnormal MRI in our study demonstrated significant associations with age <6 years and stimulated LH/FSH ratio >0.6 for predicting MRI abnormality. However, none of the predictors were robust enough to be used for decision-making regarding the necessity of MRI investigation. Similar to our observation, in the study of Mogensen et al. (9), 13 girls with newly diagnosed CNS pathology were above 6 years of age, and 6 girls were 8-9 years old. Although basal LH was higher in girls with newly diagnosed CNS lesions than in girls with a nonpathological MRI, no cut-off value was evident as values overlapped. In contrast to Chalumeau et al. (6), estradiol level was not a significant risk factor for MRI abnormalities in our study, nor in the study of Mogensen et al. (9). Due to the episodic nature of estradiol secretion in the early stages of puberty, concentrations vary widely in girls with CPP. Furthermore, commercial estradiol assays are not sensitive enough to discriminate between girls with premature thelarche and those with CPP (33).

Systematic MRI uncovered a new and causally related MRI abnormality in around 1 in every 14 girls in those <6 years old, and 1 in every 31 girls in those >6 years of age in the present study. Thus, although it is evident that the vast majority of girls with CPP undergo unnecessary MRI evaluation, if we had performed MRI only in those <6 years, 2 patients with neoplastic lesions and 1 patient who required surgery (enlarging Rathke cleft cyst) may have been missed. Hence, in the absence of reliable clinical or biochemical predictors, systematic cranial MRI seems to be the most efficient current approach to avoid missing the diagnosis of pathological CNS lesions in girls with CPP, independently of age of puberty onset and despite the low likelihood of finding a lesion requiring intervention. The question remains about whether systematic imaging is cost-effective and should be done in girls >6 years given the above data. An alternative approach would be to notify the parents of the low likelihood of finding an intracranial tumor in those >6 years and discuss pros and cons of MRI scanning to assist them in making an informed decision (34, 35).

Additional Information

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