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Central Precocious Puberty in Girls: An Evidence-Based Diagnosis Tree to Predict Central Nervous System Abnormalities

Martin Chalumeau, MD*; Wassim Chemaitilly, MD‡; Christine Trivin, PhD§; Luis Adan, MD¶||; Gérard Bréart, MD*; and Raja Brauner, MD‡

ABSTRACT. *Objective.* To identify predictors of central precocious puberty (CPP) that reveal central nervous system (CNS) abnormalities in girls with CPP.

Methods. A retrospective cohort study was conducted of all girls younger than 8 years with breast development related to CPP, seen between 1982 and 2000, in a university pediatric hospital in Paris, France. For a pilot population (186 idiopathic, 11 revealing CNS abnormalities), the accuracy of the Lawson Wilkins Pediatric Endocrine Society recommendations were evaluated. Potential clinical, radiological, and biological predictors of CNS abnormalities were assessed by univariate and multivariate analyses. A diagnosis tree aiming for 100% sensitivity for the detection of CNS abnormalities was constructed and was tested on a validation population (39 idiopathic, 3 revealing CNS abnormalities).

Results. Applying the Lawson Wilkins Pediatric Endocrine Society recommendations, 2 of 11 girls with CPP that revealed CNS abnormalities would not have been considered to require brain imaging. Independent predictors of CNS abnormalities were age at onset of puberty <6 years (adjusted odds ratio [AOR]: 6.7; 95% confidence interval [CI]: 1.5–29), lack of pubic hair at diagnosis (AOR: 7.7; 95% CI: 1.8–33), and estradiol >110 pmol/L (AOR: 4.1, 95% CI: 1.0–17). The diagnosis tree that was constructed on the basis of these predictors had 100% sensitivity and 56% specificity for the validation population.

Conclusion. The identification of girls who have CPP and require cerebral imaging seems possible on the basis of validated, simple, and reproducible predictors: age and estradiol. However, this process needs to be tested on other populations. *Pediatrics* 2002;109:61–67; *precocious puberty, brain neoplasms, epidemiology, practice guidelines, multivariate analysis.*

ABBREVIATIONS. CPP, central precocious puberty; CNS, central nervous system; LWPES, Lawson Wilkins Pediatric Endocrine Society; BMI, body mass index; SD, standard deviation; E₂, estradiol; LH, luteinizing hormone; FSH, follicle-stimulating hormone; AOR, adjusted odds ratio; CI, confidence interval.

From *INSERM U149, Epidemiological Research Unit on Women's and Children's Health, Paris, France; ‡Pediatric Endocrinology Department, §Physiology Laboratory, Université René-Descartes, Hôpital Necker-Enfants Malades, Assistance Publique-Hôpitaux de Paris, Paris, France; and ¶SESAB/CEDEBA, Centro de Diabetes e Endocrinologia do Estado da Bahia, Salvador-Bahia, Brazil.

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Reprint requests to (R.B.) Service d'Endocrinologie et Croissance, Hôpital Necker-Enfants Malades, 149, rue de Sèvres, 75743 Paris Cedex 15, France. E-mail: raja.brauner@wanadoo.fr

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In girls, precocious puberty is classically defined as breast development before the age of 8 years.^{1–5} Given the secular trend toward earlier puberty, the percentage of girls with precocious puberty rose from 2.5% in 1969⁶ to 10% in the 1990s.^{7,8} When precocious puberty is secondary to the activation of the hypothalamic–pituitary–gonadal axis, it is called central precocious puberty (CPP). CPP accounts for 89% to 98% of the cases of precocious puberty in published series.^{9–12} CPP can result from central nervous system (CNS) abnormalities, mainly hamartomas and hypothalamic tumors. Brain imaging is thus systematically recommended in girls with CPP.^{9,10,13–16}

Clinicians who deal with CPP have 2 main concerns: detection of CNS abnormalities and short final height. The risk for girls with CPP to reach a final height that is too short has been widely debated, and several authors have suggested limiting the use of gonadotropin-releasing hormone analog.^{4,5,17} Thus, a means of identifying the group of girls who have CPP and are at high risk of CNS abnormalities is essential. In hospital-based studies, CPP revealed CNS abnormalities in 8% to 33% of the girls.^{2,9–11,13,15,16,18} Reported predictors for CNS abnormalities in girls with CPP are young age at the onset of puberty,^{13,15,19} presence of pubic hair at the same time,¹³ markedly advanced bone age,^{15,19} rapid progression of puberty,^{15,19} and high plasma gonadotrophins concentrations.¹³ Unfortunately, those studies were based on small series with high frequencies of CNS abnormalities suggestive of selection bias^{13,15} or did not include appropriate statistical analysis.¹⁹ New recommendations from the Lawson Wilkins Pediatric Endocrine Society (LWPES)²⁰ and Elders et al²¹ were proposed to identify girls who are at high risk (for both CNS abnormalities and short final height), but they were mainly based on a study in which the cause of precocious puberty was not assessed.⁷

The objectives of the present study were to evaluate the accuracy of the recommendations made by the LWPES for our patients; to identify independent predictors (ie, risk factors) for CPP revealing CNS abnormalities in affected girls; and to construct and validate a diagnosis tree, based on independent predictors, aimed at identifying girls who have CPP and require brain imaging.

METHODS

Patients

All girls were seen by one of us (R.B.) between May 1982 and December 2000 at Hôpital Necker-Enfants Malades, Paris, France. This tertiary university pediatric hospital is 1 of the 4 referral centers for pediatric endocrinology in the Paris metropolitan area.

CPP was diagnosed on the basis of evidence of breast development before the age of 8 years. Premature thelarche and primary gonadal or adrenal diseases were excluded according to the diagnostic criteria described by Palmert et al.²² Patients with CPP secondary to a previously diagnosed CNS abnormality were excluded.

Measurements

Data on 20 clinical, radiological, and biological variables were collected retrospectively from the patients' records. The age at the onset of puberty was defined as the age when breast development was first noted by the patient or her parents. Other data were the values recorded at the first physical examination. Standing height was measured with a Harpenden stadiometer. Body mass index (BMI) was calculated and expressed as a z score with respect to chronological age.²³ Growth rate was expressed as standard deviation (SD) for chronological age.²⁴ Breast and pubic hair development were rated according to Tanner stages.⁶ For axillary hair, we used the same 3-stage scale as others.⁷ Bone age was assessed by 1 senior pediatric endocrinologist (R.B.).²⁵ Estradiol (E₂) was extracted from plasma with ether and measured by radioimmunoassay (Estradiol 2; Sorin Biomedica, Antony, France). The hypothalamic-pituitary-gonadal axis was investigated by measuring basal plasma luteinizing hormone (LH) and follicle-stimulating hormone (FSH) concentrations and peak stimulated (gonadotropin-releasing hormone, 100 µg/m² intravenously) LH and FSH concentrations. The LH/FSH peak ratio and the difference (Δ) between peak and basal LH and FSH values were calculated.

Patients were classified as having idiopathic CPP or CPP revealing a CNS abnormality, depending on the normality of computed tomography and/or magnetic resonance imaging of the brain and pituitary region.

Data Analysis

Statistical analyses were performed using BMDP software (BMDP Statistical Software, Los Angeles, CA) and EpiInfo software (Centers for Disease Control and Prevention, Atlanta, GA). Variables were selected when <10% of the data were missing for girls with idiopathic CPP and no data were missing for those with CPP revealing a CNS abnormality. Continuous variables were dichotomized on the basis of the rounded-off quartiles of the distribution among idiopathic CPP. The quartile with the highest frequency of CNS abnormalities was compared with the rest of the population. Tanner stages were dichotomized around the first stage of the distribution to ensure easy external reproducibility. Univariate analysis was performed using the 2-tailed Fisher exact test to evaluate the association between potential predictors and the detection of CNS abnormalities. Multivariate analysis using logistic regression (backward stepwise procedure) was conducted by entering variables identified by univariate analysis as being associated with CNS abnormalities with a degree of significance <0.20. *P* < .05 was considered statistically significant.

Diagnosis-Tree Construction

All of the above analyses were performed on a pilot set of data corresponding to patients included between 1982 and 1998. A diagnosis tree with an a priori objective of 100% sensitivity was constructed. The variables that were independently associated with CNS abnormalities were selected for the construction of the diagnosis tree. The order of appearance of the variables in the tree followed the order of data collection in clinical practice (general data followed by clinical signs then biological values). Cutoffs were modified to obtain 100% sensitivity for the diagnosis of CNS abnormalities in the pilot population and to coincide with routine clinical practice. The stability of the crude relationship with the newly modified cutoff was verified. Once 100% sensitivity was obtained (and its corollary, 100% negative-predictive value), the

specificity and positive-predictive value of the diagnosis tree were calculated for the pilot population.

Diagnosis-Tree Validation

The diagnosis tree was then applied to the validation set of patients, included between 1999 and 2000. The investigator who constructed the tree (M.C.) was not aware of the values of the variables in the validation population. The diagnosis tree was not modified after it was first applied to the validation data set. The sensitivity, specificity, and positive and negative predictive values of the diagnosis tree were calculated for the validation population.

RESULTS

Pilot Population

During the period corresponding to the pilot group, 197 girls met the inclusion criteria. Among them, 11 (6%) had CPP that revealed a CNS abnormality: hamartoma (*n* = 6), glioma (*n* = 3), angioma cavernosum (*n* = 1), and suprasellar arachnoid cyst (*n* = 1). Age distribution according to causative diagnosis is presented in Fig 1.

CPP revealed a CNS abnormality (1 glioma, 1 hamartoma) in 2 white girls (18%) who would not have been considered as requiring brain imaging according to the LWPES's recommendations.²⁰ Indeed, their puberty began after 7 years of age and was not unusually rapid: their growth rates were -1.8 and 0.5 SD, and breast development was Tanner stage 3 for both. Their bone age advances were <2.0 years (0.2 and 1.9 years). Their predicted final

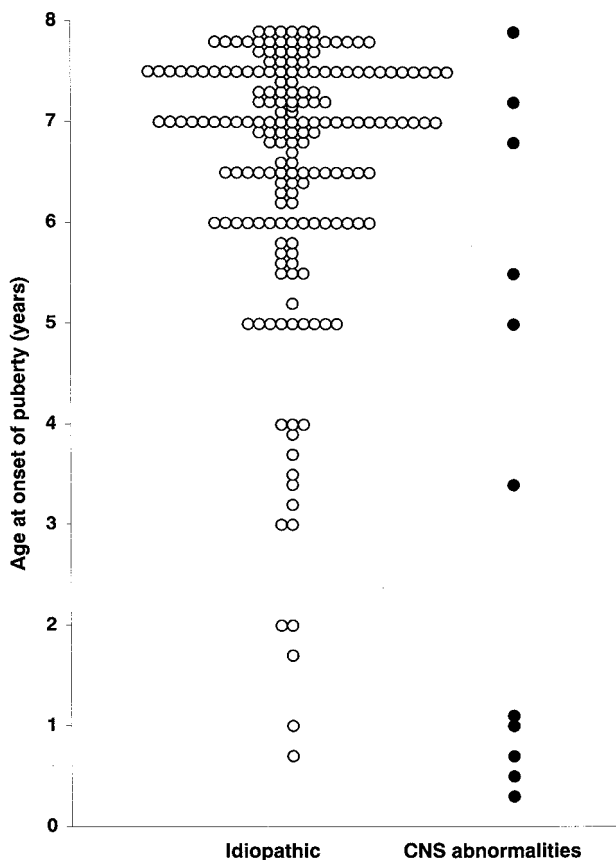


Fig 1. Age distribution at onset of puberty (ie, when breast development was first noted by the patient or her parents) in girls with CPP, either idiopathic (*n* = 186) or revealing CNS abnormalities (*n* = 11).

heights were >150 cm (161 and 159 cm), and the difference between their predicted and genetic target heights were shorter than -10 cm (-2 and -1 cm). Neither had headaches, seizures, focal neurologic deficits, or adversely affected emotional states. The patient with glioma also had a growth hormone deficiency that explained her slow growth rate and minor bone age advance.

Univariate Analyses

According to univariate analyses (Table 1), the main associations with CNS abnormalities were age at onset of puberty <6 years and lack of pubic hair at first examination. Minor but significant associations were found: E₂ >110 pmol/L, peak FSH >20 U/L, and ΔFSH >15 U/L. No significant associations were found with growth rate >3 SD, BMI <0.5 z score,

breast development greater than stage 2, axillary hair greater than stage 1, advanced bone age ≤0.5 years, basal LH >1 U/L, basal FSH >5 U/L, peak LH >15 U/L, LH/FSH peak ratio >1, and ΔLH >15 U/L.

Multivariate Analyses

After adjustment by logistic regression performed with the variables of 188 patients (including all patients with CPP revealing CNS abnormalities), only 3 variables remained independently associated with CNS abnormalities: age at onset of puberty <6 years (adjusted odds ratio [AOR]: 6.7; 95% confidence interval [CI]: 1.5–29; *P* = .01), lack of pubic hair at first physical examination (AOR: 7.7; 95% CI: 1.8–33; *P* = .004), and E₂ >110 pmol/L (AOR: 4.1; 95% CI: 1.0–17; *P* = .04).

TABLE 1. Univariate Analysis: Relationships Between Potential Clinical or Radiological Predictors and CNS Abnormalities in Girls with CPP

Variable	Idiopathic CPP (<i>n</i> = 186)		CNS Abnormalities* (<i>n</i> = 11)		OR	95% CI	<i>P</i> Value
	<i>n</i>	%	<i>n</i>	%			
Age at onset of puberty (y)							
<6	34	18.3	8	72.7	11.9	2.7–61	<10 ⁻³
≥6	152	81.7	3	27.3	1		
Growth rate (SD)							
>3	41	24.4	4	36.4	1.8	0.4–7.3	.50
≤3	127	75.6	7	63.6	1		
BMI (z score)							
<0.5	43	23.1	5	45.5	2.8	0.7–11.0	.14
≥0.5	143	76.9	6	54.5	1		
Breast (Tanner stage)							
2	88	47.6	7	63.6	1.9	0.5–8.3	.30
>2	97	52.4	4	36.4	1		
Pubic hair (Tanner stage)							
1	30	16.2	7	63.6	9.0	2.2–40	<10 ⁻³
>1	155	83.8	4	36.4	1		
Axillary hair (stage†)							
1	127	68.6	9	81.8	2.1	0.4–14	.51
>1	58	31.4	2	18.2	1		
Advanced bone age (y)							
≤0.5	39	21.7	1	9.1	2.8	0.3–60	.50
>0.5	141	78.3	10	90.9	1		
E ₂ (pmol/L)							
>110	39	22.0	6	54.5	4.3	1.1–17	.02
≤110	138	78.0	5	45.5	1		
Basal LH (U/L)							
>1	54	31.8	7	63.6	3.8	0.9–16	.05
≤1	116	68.2	4	36.4	1		
Basal FSH (U/L)							
>5	55	32.2	7	63.6	3.7	0.9–16	.05
≤5	116	67.8	4	36.4	1		
Peak LH (U/L)							
>15	47	25.3	6	54.5	3.6	0.9–14	.07
≤15	139	74.7	5	45.5	1		
Peak FSH (U/L)							
>20	32	17.2	6	54.5	5.8	1.4–24	.008
≤20	154	82.8	5	45.5	1		
LH/FSH peak ratio							
>1	50	26.9	5	45.5	2.3	0.6–8.1	.18
≤1	136	73.1	6	54.5	1		
ΔLH (U/L)							
>15	42	24.7	6	54.5	3.7	0.9–15	.07
≤15	128	75.3	5	45.5	1		
ΔFSH (U/L)							
>15	33	19.3	6	54.5	5.0	1.2–21	.01
≤15	138	80.7	5	45.5	1		

* CPP revealing a CNS abnormality.

† According to Hermann-Giddens et al.⁷

TABLE 2. Prediction of CNS Abnormalities in Girls With CPP, in the Pilot ($n = 197$) and Validation ($n = 42$) Populations, Using Either Independent Predictors Alone or the Diagnosis Tree

Model Characteristic (%)	Age <6 (Years)		Lack of Pubic Hair		E ₂ (pmol/L)				Diagnosis Tree	
					>110		>45			
	P*	V†	P	V	P	V	P	V	P	V
Sensitivity	73	67	64	100	55	67	91	67	100	100
Specificity	82	85	84	76	78‡	87	45‡	69	38	56
Positive predictive value	19	25	19	25	13	29	9	14	9	15
Negative predictive value	98	97	98	100	97	97	99	96	100	100

* Pilot population.

† Validation population.

‡ $n = 188$, E₂ was unknown for 9 girls (5%) with idiopathic CPP.

Diagnosis-Tree Construction

The sensitivities and the specificities of the 3 independent predictors for CNS abnormalities used alone are reported in Table 2. None alone or in combination (data not shown) reached the required 100% sensitivity. Thus, we modified the initial cutoffs. The 6-year age cutoff was retained because it did not seem clinically realistic to propose avoiding evaluation under this age. The cutoff around Tanner stage 1 was kept to ensure easy reproducibility. It was necessary to lower the plasma E₂ threshold to <54 pmol/L to obtain the required 100% sensitivity in combination with age. It was lowered to 45 pmol/L in light of the intermeasurement variability (SD = 3.9 pmol/L). This value represented the 45th percentile of girls with idiopathic CPP. With this threshold, the association of E₂ with CNS abnormalities was still significant (OR: 8.3; 95% CI: 1.1–179; $P = .03$). The lack of pubic hair was no longer helpful and was not used in the final diagnosis tree.

In the high-risk part of the first branch of the final diagnosis tree (ie, patients <6 years), 19% (8 of 42) of CPP revealed CNS abnormalities (Fig 2). We thought we had identified a very high-risk population for whom brain imaging should systematically be performed, and thus we stopped the segmentation of this branch. In the low-risk branch, a second segmentation was applied using the 45-pmol/L E₂ cutoff. The final decision tree had 38% specificity and 9% positive predictive value (Table 2). By using it to select patients for brain imaging, no CNS abnormality would have been missed and 67 (38%) noncontributive imagings would have been avoided.

Diagnosis-Tree Validation

Among the 42 girls with CPP in the validation population, CPP revealed a CNS abnormality (hamartoma) in 3 (7%). The new sensitivities and specificities of each of the 3 predictors alone were calculated for these girls (Table 2). The diagnosis tree

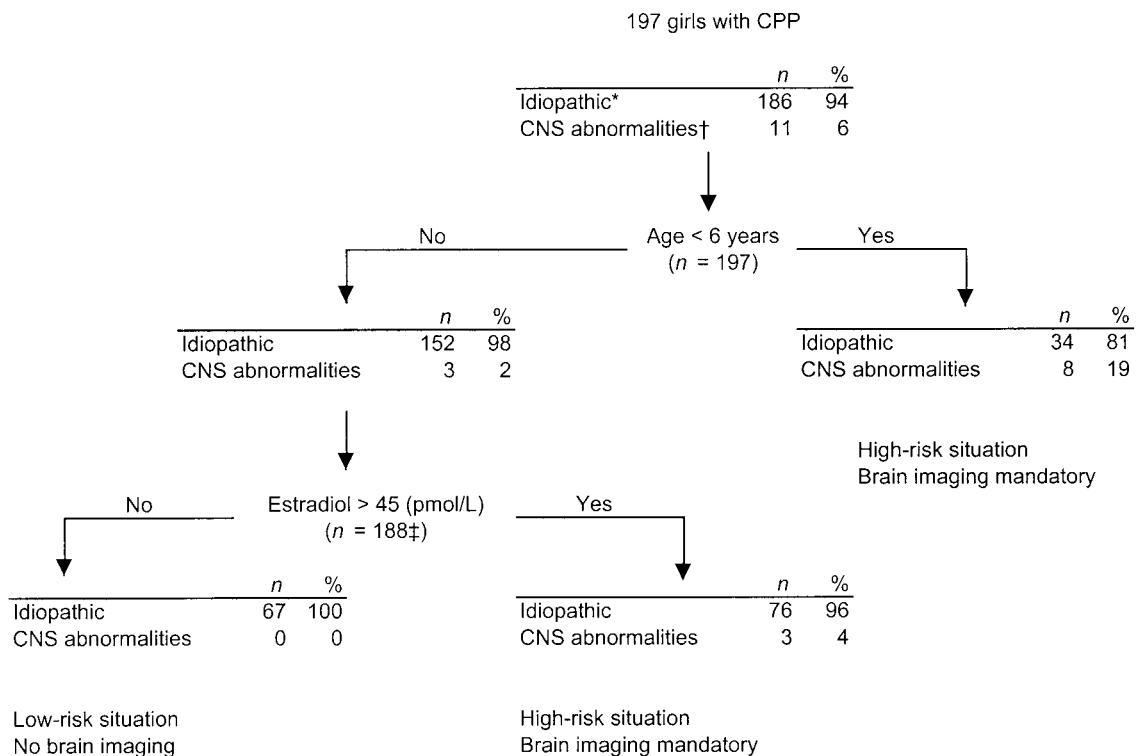


Fig 2. Diagnosis tree constructed with the pilot population to predict low or high risk of CNS abnormalities for girls with CPP. *Idiopathic CPP; †CPP revealing CNS abnormalities; ‡E₂ was unknown for 9 girls (5%) with idiopathic CPP.

had 100% sensitivity, 100% negative predictive value, 56% specificity, and 15% positive predictive value (Fig 3, Table 2). By applying it to select patients for brain imaging, no CNS abnormality would have been missed and 22 (56%) noncontributive imagings would have been avoided.

DISCUSSION

We confirmed that the principal predictor of a CNS abnormality in girls with CPP was young age at the onset of puberty, as was suspected by others.^{13,15,19} However, this predictor cannot be used alone: extremely early CPP can be idiopathic, and CPP between 7 and 8 years of age can be the only element revealing CNS abnormality, as shown in our patients. We also confirmed that girls with CNS abnormalities had more biologically advanced puberty with significantly higher E_2 , peak and Δ FSH concentrations and tendencies toward significantly higher basal LH and FSH and peak and Δ LH concentrations.¹³

A new simple clinical predictor of CNS abnormalities in girls with CPP was identified in our study: the lack of pubic hair at the time of diagnosis. The relationship between the lack of pubic hair and a CNS abnormality remained strong after taking into account potential confounders, such as age or biological findings. Cacciari et al¹³ found an opposite result based on a very small population ($n = 15$). Our finding is in agreement with a former description of girls with CPP as a result of hamartoma without evidence of adrenarche.²⁶ LH-releasing hormone-containing fibers have been observed within hamartoma tissues in patients with CPP.^{27,28} However, the relationship between the lack of pubic hair at diagnosis and CNS abnormalities other than hamartoma was also strong and significant (OR: 20.7; 95% CI: 2.1–500; $P = .002$). Thus, the direct secretion of LH-

releasing hormone by CNS abnormalities may not be the only explanation for the dissociation between gonadarche and adrenarche in patients with CPP caused by a brain tumor or malformation.

A new approach to identify girls who have CPP and require brain imaging has been described herein. This selection is based on 2 simple and reproducible criteria: age and plasma E_2 concentrations. Our diagnosis tree was constructed with the aim of obtaining 100% sensitivity. As the classical approach to the diagnosis of CPP includes systematic brain imaging,^{9,10,13–16} it did not seem ethical to us to propose a diagnosis tree with sensitivity below 100%. Given this imposed sensitivity and the lack of highly discriminate criteria, the specificity is low (approximately 40%–55%), but these levels of sensitivity and specificity offer the opportunity to avoid safely one third to one half of brain imagings.

We did not use automatic strategies to create our diagnosis tree by segmentation analysis, such as those provided by software (eg, Answer Tree software [SPSS Inc, Chicago, IL]).²⁹ We excluded variables that were not independently associated with CNS abnormalities to avoid the use of nonrobust predictors. The order of appearance of variables in the diagnosis tree was modeled on the order of data collection in clinical practice. The cutoff values were imposed to fit with clinical concerns (age at onset of puberty), to offer good clinical reproducibility (Tanner stage for pubic hair), or to ensure 100% sensitivity (E_2).

Because of the retrospective design of our study, some variables (ethnicity, age at menarche of patient's mother, weight gain, etc) had too many missing data and were excluded from the analysis. This exclusion did not modify the univariate analysis results, but multiple logistic regression might have suffered from incomplete adjustment.

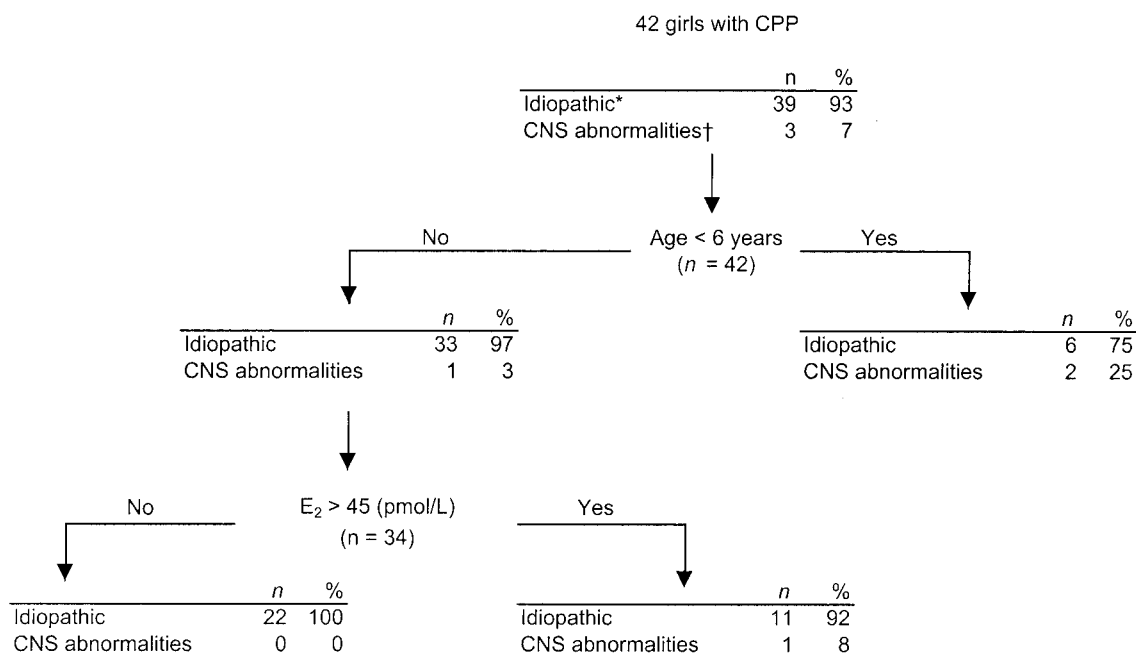


Fig 3. Distribution of the validation population along the diagnosis tree constructed with the pilot population. *Idiopathic CPP; †CPP revealing CNS abnormalities.

The frequency of CNS abnormalities (6%) and the histologic distribution of lesions found in our study are close to that (8%) found in the large study by the Italian collaborative group.⁹ This frequency is much lower than those reported in older smaller studies, which probably suffered from recruitment bias.^{2,10,11,13,15,16,18} However, because our population consisted of girls with CPP rather than girls who had breast development, were younger than 8 years, and were seen in office-based settings, our results cannot be generalized to this latter population.

A prognosis or diagnosis model should not be applied in clinical practice before a well-defined validation process has been completed.³⁰ We conducted a first external validation using a small sample of patients from the same center as the pilot population. The next step will be to test these results on a large sample of patients seen outside our hospital. The need for external validation is particularly true for models involving puberty for which marked racial variations exists.^{7,8} The validation should start with the evaluation of the stability of the predictors established in our patients. For example, an attempt was made to validate our findings using a population of girls with CPP in Salvador-Bahia, Brazil. It was unsuccessful because their age at onset of puberty was younger, their pubic hair was more prevalent, and their plasma E₂ concentrations were higher than in our patients. However, the advantage of our diagnosis tree is its simplicity. Clinicians can modify thresholds according to the distributions in their populations of girls with CPP. However, each change must be validated before being routinely applied in clinical practice.

There is increasing concern about the quality of practice guidelines developed by specialty societies.³¹ The LWPES's recommendations were formulated to identify girls who have CPP and need evaluation for risk of both CNS abnormalities and short final height.²⁰ Their conclusions were derived mainly from a study in which the cause of precocious puberty was not assessed.⁷ Those new recommendations raised some concerns.³¹⁻³³ Given that they were designed to apply to American girls, we found that 2 of our 11 French patients with CPP revealing CNS abnormalities (including 1 glioma) would not have been identified as requiring brain imaging. Among 163 Italian girls who had CPP and were between the ages of 7.0 and 7.9 years, reported by Cisternino et al,⁹ 2 hamartomas and 1 tumor of the fourth ventricle were revealed by CPP. The real impact of the LWPES's recommendations should now be tested on American girls.

We agree with the LWPES that the age threshold of 8 years for breast development is based on outdated studies,²⁰ as clearly demonstrated in the United States by Herman-Giddens et al⁷ and in China by Huen et al.⁸ It is probably true in many other countries. We also agree that a systematic approach using invasive dynamic biological tests and brain imaging in all cases of breast development before 8 years of age is not cost-effective. Thus, there is an urgent need for population-based studies including biological work-up and brain imaging to

exclude premature thelarche, primary gonadal precocious puberty, and CPP revealing CNS abnormalities. Predictors for short final height and/or CNS abnormalities, identified by rigorous statistical analysis, need to be established.

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UNDERPAID PHILANTHROPISTS

“When someone works for less pay than she can live on—when, for example, she goes hungry so that you can eat more cheaply and conveniently—then she has made a great sacrifice for you; she has made you a gift of some part of her abilities, her health, and her life. The ‘working poor,’ as they are approvingly termed, are in fact the major philanthropists of our society. They neglect their own children so that the children of others will be cared for; they live in substandard housing so that other homes will be shiny and perfect; they endure privation so that inflation will be low and stock prices high. To be a member of the working poor is to be an anonymous donor, a nameless benefactor, to everyone else.”

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Submitted by Student

Central Precocious Puberty in Girls: An Evidence-Based Diagnosis Tree to Predict Central Nervous System Abnormalities

Martin Chalumeau, Wassim Chemaitilly, Christine Trivin, Luis Adan, Gérard Bréart and Raja Brauner

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