Prevalence and clinical characteristics of isolated forms of central precocious puberty: a cohort study at a single academic center

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Abstract

Objective: Isolated central precocious puberty (CPP) includes sporadic, familial and adoption-related forms, and the characterization of its etiology is challenging. This study investigated the prevalence and clinical characteristics of isolated CPP.

Design and methods: This observational cohort study included all patients ($n = 395$) with CPP included in the database of a single academic pediatric care center over a period of 11.5 years.

Results: In total, 332 of the 395 patients (84%) had isolated forms of CPP; the proportion of male patients was lower in this group than for non-isolated CPP (4 vs 33%, $P < 0.0001$). These patients had sporadic ($n = 228$, 68.5%), familial ($n = 82$, 25%) or adoption-related ($n = 22$, 6.5%) forms. Clinical characteristics at diagnosis were similar between groups, but girls with sporadic CPP were older at referral than those with familial or adoption-related CPP ($P < 0.02$), and birth weight SDS was lower in adopted patients than in those from the sporadic and familial groups ($P < 0.01$). In the 72 families containing patients with familial forms, both recessive and dominant transmissions were observed between first-degree relatives. Potential maternal or paternal transmission was identified in two-thirds of the studied families, in similar proportions. An autosomal dominant mode of transmission with low penetrance was suggested by the high proportion of affected parents (33 of the 72 families, 46%). Clinical presentation was similar whatever the mode of inheritance.

Conclusion: These findings highlight the need for careful monitoring of the various forms of CPP. Future studies should explore pathophysiological mechanisms, particularly for familial forms.

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CPP is defined as premature activation of the hypothalamic-pituitary-gonadal axis, with the development of secondary sexual characteristics before the age of 8 years in girls and 9.5 years in boys. Most patients have isolated forms (sporadic, familial or related to adoption) with no known underlying disorders and are considered to have ‘idiopathic CPP’ with no identifiable cause. Non-isolated CPP is less frequent and caused by acquired

or congenital hypothalamic lesions visible on MRI or associated with various complex genetic and/or syndromic disorders (1, 2).

Pubertal timing is influenced by complex interactions of genetic, nutritional, environmental and socioeconomic factors (3, 4). Evidence of the genetic regulation of pubertal timing is provided by the strong correlation of age at onset of puberty within families and ethnic groups

and the stronger correlation between monozygotic than between dizygotic twins (5). In recent years, significant progress has been made toward understanding the molecular mechanisms underlying the neuroendocrine control of puberty in humans (6, 7, 8). Given recent findings concerning the genetic causes of CPP, mostly for syndromic forms (2) or isolated familial CPP, predominantly paternally transmitted with a loss of function of two imprinted genes (*MKRN3* and *DLK1*) (9, 10), a clear knowledge of the different clinical forms of CPP is essential and could help to improve our understanding of the pathophysiological mechanisms underlying the precocious onset of puberty (11).

A few groups have described the epidemiological features of isolated CPP at their own institution (12, 13), at multiple institutions (14) or based on national registries, regardless of the form of CPP (15, 16, 17). These studies have separately reported a much higher incidence in girls than in boys (18, 19, 20, 21), in sporadic and familial forms (12) or in adopted children.

The aim of this study was to investigate the different types of isolated CPP phenotypes and their prevalences in a large cohort of consecutive patients with CPP, and to determine whether clinical characteristics at diagnosis differed between the sporadic, familial and adopted groups.

Patients and methods

Patients

This observational cohort study included all Caucasian and non-Caucasian patients identified as having CPP in the database of the Pediatric Endocrinology Department of Robert Debré University Hospital in Paris over a period of 11.5 years, from January 2006 to June 2017. CPP was diagnosed on the basis of breast development before the age of 8 years in girls and testicular enlargement before the age of 9.5 years in boys, together with evaluations of serum gonadotropin-releasing hormone (GnRH) activation, based on basal serum LH levels or, much more frequently, after stimulation with exogenous GnRH or the occurrence of menarche before the age of 10 years. We excluded patients who had previously undergone brain irradiation or who had been exposed early to sex steroids.

Study protocol

Clinical data for the patients were obtained from their medical records. Demographic characteristics, including personal medical history and known associated abnormalities (e.g. neurodevelopmental or syndromic phenotypes with or without chromosomal abnormalities), sex, adoption status (living with biological or adoptive parents), consanguinity, age at first pubertal symptoms, age at first evaluation, bone age, height, weight, pubertal stage and biological data concerning puberty onset at diagnosis were recorded, together with brain MRI findings. Parental reports of the timing of puberty in first-degree (mother, father, siblings), second-degree (grandparents, uncles and aunts) and third-degree (cousins) relatives were assessed. Data for more distantly related individuals were occasionally provided by the parents. If the father never attended hospital visits with his child, the mother was asked to ask the father and/or paternal grandmother about the timing of puberty, with a view to identifying cases of CPP within the paternal pedigree. Evidence for a familial history of CPP was assessed based on age at menarche for girls (before or at 10 years old being considered precocious), and the age or timing, during or after primary school, of growth spurts or growth completion for boys, as the assessment of genital development is more complex and subjective in boys. The mothers were also asked to ask their own mothers (the maternal grandmothers) about pubertal timing in the maternal pedigree. Patients were classified as Caucasian, non-Caucasian or of unknown ethnicity. CPP cases were assigned to two groups on the basis of cause (isolated and non-isolated CPP) and then to the following categories: isolated CPP was split into sporadic CPP, familial CPP and adopted patient subgroups, and non-isolated CPP was split into a group of patients with pathological CNS features, with hypothalamic lesions on brain MRI, and a group of patients with without hypothalamic lesions on MRI, with associated syndromes and chromosomal or molecular disorders. The patients with non-isolated CPP were described in a previous study (11).

The study protocol was approved by the Ethics Review Committee for Biomedical Research Projects of Robert Debre University Hospital (no. 2014-158). Informed consent was obtained from the parents.

Methods

Precocious puberty (PP) has been defined as the onset of clinical signs of puberty before the age of 9.5 years

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in boys (testicular enlargement) and before the age of 8 years in girls (breast development), or as the occurrence of menarche before the age of 10 years. For familial forms (at least two members of the family affected), the mode of CPP inheritance was assessed and classified into four groups: (I) affected siblings only, (II) maternally (a) or paternally (b) transmitted, (III) potentially maternally (a) or potentially paternally (b) transmitted (mother or father without CPP, but CPP reported within the maternal, or paternal pedigree), (IV) more complex forms of inheritance. Inheritance was then classified as dominant (if shown to be transmitted from parents to offspring, or from generation to generation) or recessive (if CPP was observed in siblings or cousins within the same generation, only). Non-Caucasian (non-white) patients were defined as having at least one parent from Asia, sub-Saharan Africa (North African patients were considered to be Caucasian), Oceania, or Latin America.

The hypothalamic-pituitary-gonadal axis was assessed by measuring basal gonadotropins and gonadotropin responses in the GnRH stimulation test (serum LH and FSH concentrations determined at baseline and 20, 40, 60 and 90 min after the i.v. bolus administration of 100 µg/m² GnRH. Central PP was diagnosed if the LH peak >5 IU/L and/or if basal LH concentration >0.3 IU/L, and on the basis of plasma testosterone concentrations in boys and plasma estradiol concentrations in girls. Girls also underwent pelvic ultrasound scans. A longitudinal uterus diameter of more than 35 mm, a pear-shaped uterus, and endometrial thickening were considered to be signs of estrogenic stimulation.

Height, and BMI (weight (kg)/height (m²)) were expressed as the SDS for sex and chronological age (22). Pubertal development (visual inspection and palpation of breast development in girls, and testis measurement in boys) was assessed by determining Tanner stage. Bone age was determined by the Greulich and Pyle method. Target height was calculated from mid-parental height. Each feature of the syndromic phenotypes was carefully assessed, separately. Brain MRI was performed for all patients at CPP diagnosis, to rule out non-isolated CPP. All MRI images (1.5 Tesla Magnet Philips Intera, Philips Medical Systems, The Netherlands) were reviewed by the same investigator. Sagittal and coronal thin (1.5 mm) slices of the hypothalamic-pituitary area were acquired with a gradient echo T1-weighted sequence and coronal slices of the brain were acquired with a T2-weighted sequence.

Hormone assays

Serum FSH and LH concentrations were determined in immunochemiluminescence assays (Siemens Healthcare SAS, Saint-Denis, France). Serum testosterone and estradiol concentrations were determined by RIA (RIA Testosterone Direct, Beckman Coulter-Immunotech, Villepinte, France and EST-US-CT, Cisbio Bioassays, Gif-sur-Yvette, France). The intra-assay coefficients of variation (CV) were <3.5% for FSH, <4% for LH, <6% for testosterone and <10% for estradiol, and the inter-assay CVs were < 6.5% for FSH, <6% for LH, <12% for testosterone, and <13.5% for estradiol.

Statistical analysis

The results are expressed as numerical values (percentages) for categorical variables and medians (25–75th percentiles) for continuous variables. Between-group comparisons were performed with Chi-squared tests for categorical variables and non-parametric Mann–Whitney or Kruskal–Wallis tests for continuous variables. All statistical analyses were carried out with SAS software, version 9.12 (SAS Institute Inc., Cary, North Carolina).

Results

In total, 395 children were diagnosed with CPP during the study period: 361 girls (91%) and 34 boys. These patients were assigned to two groups according to the isolated ($n=332$, 84%) or non-isolated ($n=63$, 16%) nature of their CPP. The proportion of male patients with isolated forms of CPP was significantly lower than the proportion with non-isolated CPP forms, at 4% and 33%, respectively ($P < 0.0001$). The 332 patients with isolated forms of CPP comprised 228 (68.5%) patients with sporadic forms, 82 (25%) patients from 72 families with familial forms and 22 (6.5%) adopted children (all but one adopted from abroad). The sex ratio was similar for the sporadic and familial forms of CPP. All the adopted patients with CPP were girls (Fig. 1).

The clinical characteristics of the 319 girls (boys were excluded from the analysis because they were too few in number, $n=13$) with isolated forms of CPP at the time of CPP diagnosis are shown in Table 1, by group (sporadic, familial or adoption-related). Birth weight for gestational age (SDS) was lower in adopted patients ($P < 0.01$), and the proportion of non-Caucasian patients was slightly higher among adopted patients than among patients

Figure 1

Flow chart of the study.

with sporadic or familial forms of CPP. Girls with sporadic forms of CPP were referred at later ages for CPP diagnosis than those from the familial and adopted groups: 8.3 (7.7; 8.8), 8.1 (7.5; 8.8) and 8.0 (6.6; 8.3) years, respectively ($P < 0.02$). Bone age/chronological age ratio was lower in adopted patients than in girls with sporadic and familial forms of CPP ($P < 0.04$). Other clinical characteristics were similar between groups.

The pedigrees of the families presenting familial forms of CPP are shown in Fig. 2. Consanguinity was observed in four families (families 11, 27, 33 and 60). Most familial cases were seen in families with two affected members ($n=45$ patients from 43 families) but 29 families had three or more affected members. Both recessive and dominant modes of inheritance were observed. There were 16 families in which only siblings were affected and 33 families with affected parents and offspring. More distantly related affected family members were reported in 40 families, with 24 second-degree relatives and 23 third-degree relatives affected (with or without affected siblings within the family). Among familial forms, maternal transmission was more frequent than paternal

transmission. However, the proportions of transmissions considered to be potentially maternal or potentially paternal were similar, with these forms affecting two-thirds of the studied families. An autosomal dominant mode of transmission with incomplete penetrance was suggested by the high proportion of parents affected (33 of the 72 families, 46%). However, other modes of inheritance with recessive transmission might also be involved for familial cases in families with only affected siblings, and even more complex modes of transmission may operate in families with affected members in multiple generations without clear parent-to-child transmission in siblings. However, whatever the mode of inheritance, CPP was much more frequent in girls than in boys. No difference in clinical characteristics (such as those studied Table 1) was found between modes of inheritance in girls with familial forms of CPP (not studied in boys due to the limited number of male patients, $n=4$; data not shown). However, as expected, menarche occurred at a significantly younger age in the mothers of girls with familial CPP considered to be maternally or potentially maternally transmitted, than in those of patients with affected siblings only, with paternally or potentially paternally transmitted CPP or with a more complex mode of inheritance: 10.0 (9.0–12.0) vs 13.0 (11.5; 14.5), 12.5 (11.3; 13.5), and 11.3 (9.5; 13.3) years, respectively ($P < 0.0001$).

Discussion

This observational cohort study in well-characterized patients with CPP managed at a single academic center provides extensive data for various clinical presentations of isolated CPP. Overall, 84% of the patients in this cohort had isolated forms of CPP. One of the key contributions of this study is the prevalence analysis of cases of sporadic (68.5%), familial (25%) and adoption-related (6.5%) CPP in the largest group of patients with isolated CPP ever studied. Another interesting finding was the sex dependence of penetrance, with a lower proportion of boys presenting isolated than non-isolated forms of CPP, and the significantly younger age at referral for patients with familial or adoption-related forms than for those with sporadic forms, potentially reflecting the concerns of parents about the higher risk of CPP (23) leading them to pay attention to the first clinical signs of puberty in their offspring and resulting in more urgent referral than for cases not previously informed about CPP. To our knowledge, no study assessing the clinical characteristics of isolated and idiopathic CPP in a large population of

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Table 1 Clinical characteristics of the girls at the time of isolated CPP diagnosis, by group (sporadic, familial or adoption-related). Values are expressed as median $\pm$ quartiles, or as *n* (%).

	Sporadic, <i>n</i> = 219	Familial, <i>n</i> = 78	Adopted, <i>n</i> = 22
Gestational age (wk) ^a	39 (38; 40)	39 (38; 40)	38 (37; 41)
Birth length (SDS) ^b	-0.1 (-1.0; 0.5)	-0.1 (-0.9; 0.5)	-0.7 (-3.0; -0.4)
Birth weight (SDS) ^c	-0.4 (-1.0; 0.4)	0.0 (-0.8; 0.6)	-1.3 (-2.5; 0.1)*
Ethnicity, <i>n</i> (%)			
Caucasian	50 (22.8)	30 (38.5)	3 (13.6)
Non-caucasian	127 (58.0)	43 (55.0)	18 (81.8)
Unknown	42 (19.2)	5 (6.5)	1 (4.6)
Age at evaluation (years)	8.3 (7.7; 8.8)	8.1 (7.5; 8.8)	8.0 (6.6; 8.3)**
Age at puberty onset (years)	7.0 (6.5; 7.5)	7.0 (6.0; 7.5)	7.4 (5.9; 7.6)
Tanner Stage at evaluation, <i>n</i> (%)			
2	54 (25)	23 (29)	10 (48)
3)	117 (55)	44 (56)	11 (52)
4	27 (13)	9 (12)	0 (0)
5	15 (7)	2 (3)	0 (0)
Target height (SDS)	0.5 (-0.5; 1.3)	0.0 (-0.7; 1.2)	ND
Height (SDS)	2.6 (1.6; 3.4)	2.2 (1.5; 3.1)	1.4 (0.3; 2.7)
BMI (SDS)	1.3 (0.4; 2.5)	1.7 (0.5; 2.3)	0.7 (-0.1; 1.6)
Bone age/chronological age (years) ratio	1.5 (1.4; 1.6)	1.5 (1.4; 1.7)	1.4 (1.3; 1.6)***
LH peak (IU/L) ^d	11.6 (7.0; 21.3)	14.0 (7.6; 31.7)	10.6 (6.5; 14.2)
LH /FSH peak ratio	1.1 (0.6; 1.6)	1.1 (0.6; 1.9)	0.9 (0.5; 1.5)
Estradiol (pg/mL)	12.0 (6.0; 23.0)	13.0 (6.0; 26.0)	10 (5.0; 23.0)

SDS: standard deviation score **P* < 0.01; ***P* < 0.02; ****P* < 0.04.

Number of missing data: ^a*n* = 47; ^b*n* = 67; ^c*n* = 48; ^dAn LHRH stimulation test was not performed in 12 girls diagnosed with CPP on the basis of breast development before the age of 8 years and in 30 girls diagnosed with CPP on the basis of menarche before the age of 10 years. All these girls had basal serum LH concentrations $\geq$ 0.8 IU/L.

patients classified into these three subgroups (sporadic, familial and adopted groups) has ever been reported, as previous epidemiological studies have analyzed patients either as a total population (13, 19, 24) or have focused on the different subgroups separately (12, 14).

A positive family history of CPP was found in 25% of patients. Our estimate of the prevalence of the familial form is consistent with the findings of the most comparable previous study of patients with isolated CPP, which included 156 patients in total, 43 of whom (27.5%) had a familial form; however, in this previous study only sporadic and familial cases were included, with adoption-related cases being excluded (12). Another study analyzed the characteristics of familial forms in a mixed group of early and precocious puberty cases (25). This discrepancy may have introduced bias into the estimates of various characteristics. However, predominantly maternal transmission was observed in these two previous studies, whereas we found that the proportions of potentially maternal and potentially paternal transmission were similar.

Our findings are consistent with those of these two previous studies in terms of the prediction of autosomal dominant inheritance with incomplete, sex-dependent penetrance, as demonstrated by the very small number

of affected male individuals. Autosomal recessive transmission is also possible in families including only affecting siblings, and consanguinity was reported in four families. The observed patterns of transmission may also result from genetic heterogeneity.

Support for the involvement of genetic factors in the pathogenesis of isolated CPP (previously known as idiopathic CPP) was provided by recent studies implicating loss-of-function mutations of two paternally expressed imprinted genes, encoding Makorin RING-finger protein 3 (*MKRN3*) and (less frequently) Delta-like homolog 1 (*DLK1*), in CPP pathogenesis, consistent with a crucial role of these proteins in early puberty events (9, 10). A high frequency of metabolic alterations, such as overweight/obesity, hyperlipidemia and early-onset type 2 diabetes, has been reported in young adult patients with *DLK1* mutations (26). Heterozygous gain-of-function mutations have also been observed in both the kisspeptin gene and the gene encoding its receptor, *KISS1R*, but these mutations account for only very rare cases (27, 28). CPP due to *MKRN3* and *DLK1* defects displays a pattern of inheritance consistent with maternal imprinting. Pathogenic *MKRN3* variants have been found in a few families, confirming that CPP can be inherited as a monogenic disorder with complete penetrance (9).

Figure 2

Pedigrees in the 72 families with members displaying isolated CPP. Individuals with black symbols have isolated CPP. Arrows indicate the 82 probands investigated in this cohort. Group I corresponds to families with affected siblings only. Group II: (a) maternally inherited; (b) paternally inherited CPP. Group III (a) potentially maternally inherited; (b) potentially paternally inherited. Group IV, with more complex inheritance.

MKRN3 loss-of-function variants are currently the most frequent known cause of paternally inherited familial CPP (29, 30). However, many other families were negative for *MKRN3* defects, as expected in families with maternal transmission, but also in families with possible recessive or more complex transmission. This study confirms that other genes linked to CPP with complete penetrance remain to be discovered. Other imprinted genes, epigenetic modifications and/or environmental factors may also be involved (31, 32). The *Lin28B* gene and the paternally imprinted *KCNK9* gene have been reported to be associated with menarche timing, along with many other genes (7, 33). Rare variants of *LIN28B* and *KCNK9* have been considered as potential monogenic causes of CPP, although no such variants have yet been identified in CPP cases (34). An association between *Kiss1/GPR54* pathway gene polymorphism and the risk of early puberty or CPP has been reported, and should be investigated in other large populations (35, 36). All genes associated with age at menarche may be considered as candidate genes for CPP. Very large gene defects may lead to monogenic CPP, whereas more common variants would favor the complex transmission of CPP. Our findings highlight the need to develop research strategies suitable for polygenic or multifactorial CPP, in addition to monogenic CPP.

BMI (SDS) was similar in the sporadic, familial, and adopted cases of CPP and is therefore unlikely to be a determinant useful for distinguishing between the mechanisms of familial and sporadic cases. However, changes in BMI from birth to presentation in adopted patients, as illustrated by the lower birth weight for gestational age in our cohort, may have contributed to the early onset of puberty.

One of the major strengths of this study is the inclusion of all patients from a defined population for whom comprehensive data were collected at a single pediatric clinical center, making it possible to evaluate the contributions of all demographic, clinical and biological characteristics. We were, therefore, able to evaluate subgroups of individuals with different forms of isolated CPP. The main limitations of this study were the observational nature of the retrospective data collection and the parental reporting of pubertal development within families, with doubts about the validity of these data, particularly for boys and for the paternal pedigree (37, 38). Despite the inclusion of all patients with CPP, each group was small, particularly for boys, and our data provide no further insight into the clinical characteristics of the patients in the groups studied. Finally, the proportion of familial forms may have been underestimated, because

some patients may erroneously have been considered to have sporadic forms because the parents were unaware of other cases within the family, or because the index case was the first child of the family to be affected, or because their siblings were too young to have experienced CPP.

In conclusion, the results of this observational study highlight the complex interactions between multiple familial (probably genetic, at least in some cases, with genetic heterogeneity, involving many mode of transmission), ethnic, metabolic and environmental factors in precocious puberty in patients with similar clinical features of CPP. In most cases of isolated CPP, particularly in girls, CPP is considered idiopathic, but careful clinical and molecular monitoring could lead to the characterization of recently elucidated genetic factors, with a predominance of cases affected by mutations of the *MKRN3* gene in paternally transmitted forms. Additional studies are required to characterize genes associated with the maternal transmission of CPP, such cases being at least as frequent, and possibly even more frequent than paternally inherited cases. The clinical implications remain limited but additional studies are required, to investigate metabolic function in the longer term, with a view to determining potential health alterations within subsets of patients related to the pathophysiology of CPP (39).

Declaration of interest

J Léger is an editor of the journal (European Journal of Endocrinology). The other authors have no conflicts of interest relevant to this manuscript to disclose.

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