Familial Central Precocious Puberty Suggests Autosomal Dominant Inheritance

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The prevalence of precocious puberty is higher in certain ethnic groups, and some cases may be familial. The aim of this study was to investigate the mode of inheritance of familial precocious puberty and to identify characteristics that distinguish familial from isolated precocious puberty. Of the 453 children referred to our center for suspected precocious puberty between January 1, 1997, and December 31, 2000, 156 (147 girls and 9 boys) were found to have idiopathic central precocious puberty, which was familial in 43 (42 girls and 1 boy) (27.5%). Data of the familial and sporadic cases were compared. The familial group was characterized by a significantly lower maternal age at menarche than the sporadic group (mean, 11.47 ± 1.96 vs. 12.66 ± 1.18 yr; P = 0.0001) and more advanced puberty at admission (Tanner stage 2, 56.5% vs. 78.1%; P = 0.006). Segregation analysis was used to study the mode of inheritance. The segregation ratio for precocious puberty was 0.38 (0.45 after exclusion of young siblings) assuming incomplete penetrance and 0.58 (0.65 after exclusion of young siblings) assuming complete ascertainment. These results suggest autosomal dominant transmission with incomplete, sex-dependent penetrance. (J Clin Endocrinol Metab 89: 1794–1800, 2004)

IN A 1997 STUDY in pediatric practices, Herman-Giddens et al. (1) demonstrated that puberty may occur at an earlier age than previously thought, with a rate of early puberty four times higher in African-American girls than in Caucasian girls. This observation suggested a genetic regulation of the timing of puberty. Some pediatric endocrinologists believe that the pubertal pattern may be influenced by familial trends, such that families with one member with precocious puberty have a higher than normal probability of having another. However, scientific support for this assumption remains sparse. We found only a few published descriptions of cases of familial central precocious puberty (2–6) and only one study (3) of the prevalence of familial cases in a series of 58 patients with central precocious puberty.

In the present study, we sought to determine the mode of inheritance of familial precocious puberty (FPP) in families with central precocious puberty and to identify specific clinical or laboratory features that distinguish familial from sporadic cases. We also calculated the prevalence of FPP at our tertiary care center in a given period of time.

Patients and Methods

Patients

Of the 453 children evaluated in our clinic for precocious secondary sexual development between January 1, 1997, and December 31, 2000, 156 were found to have idiopathic central precocious puberty. The rest presented with precocious adrenarche (n = 101), early puberty (n = 89), premature thelarche (n = 58), obesity associated with pseudothelarche (n = 19), and other diagnoses (n = 26); four were lost to follow-up. The diagnosis of precocious puberty was based on the presence of secondary sexual characteristics before age 8 yr in females and 9 yr in males. In girls, central precocious puberty was diagnosed on the basis of clinical characteristics, including appearance of breast buds before 8 yr of age accompanied by the presence of one or more of the following findings: menarche, pubic hair, accelerated growth velocity, or bone age greater than 2 sd above chronological age. When the clinical picture was not obvious, the patients were followed for at least 6 months before the diagnosis was made. Adopted girls were excluded, as were girls with chronic disease, bone dysplasia, organic brain disease, congenital adrenal hyperplasia or other endocrinological abnormalities, and girls who had received radiation therapy and/or chemotherapy.

Written informed consent was obtained from all families. The study was approved by the institutional human research committee.

Methods

At the first visit, the pedigree was determined, detailing medical illnesses and timing of puberty in family members. The parents completed a structured questionnaire including items on puberty in first-, second-, and third-degree relatives, and they were asked to contact directly the children’s grandparents, aunts, uncles, and cousins to determine the age of puberty directly from them. We collected the data by contacting the parents by phone. First-degree relatives were defined as mother, father, brother(s), and sister(s); second-degree relatives as grandparents, aunt(s), and uncle(s); and third-degree relatives as cousins. Females were asked about age at appearance of breast buds and age at menarche and males about age at onset of pubertal changes and age at initiation of full-face shaving. Those who met the following criteria were included in the study group of FPP: 1) presentation with gonadotropin-dependent central precocious puberty, as described above; and 2) at least one of the following: menarche at age 10 yr or earlier in a first-, second-, or third-degree female relative; clinically documented precocious puberty, as described above, in a first-, second-, or third-degree relative; or full puberty, including full facial shaving, earlier than age 13 yr in a first-, second-, or third-degree male relative. [For Jewish males, age 13 (bar mitzvah) is a significant and well-remembered milestone.] Girls with idiopathic central precocious puberty without a family history were considered to have sporadic precocious puberty (SPP). All patients underwent clinical, biochemical, and bone age evaluation on admission. Pubertal stage was determined according to Marshall and
Segregation analysis

Segregation analysis was performed to study the mode of inheritance in the patients with FPP. To minimize inaccuracies due to recall bias in third-generation relatives (grandparents), we used only two generations for the segregation analysis. Relatives who claimed to have had early puberty but had inaccurate recall and relatives who had early but not precocious puberty (such as mothers with menarche at age 10.5 yr) were marked in gray in the pedigree charts and were not considered as having precocious puberty in the segregation analysis. Brothers under the age of 9 yr and sisters under the age of 8 yr at the time of the family study were excluded because they were too young to determine the presence of precocious puberty. The segregation analysis was done twice, once assuming complete ascertainment and once assuming incomplete ascertainment using the single incomplete method (12). Each of the above analyses was also done twice, once including young siblings as unaffected and once excluding them. Owing to the female predominance, we also performed a separate segregation analysis for females, using the same method.

Penetration was calculated using data obtained from three generations.

Statistical analysis

Statistical analysis was done with BMDP software (New System version, Statistical Solutions, Cork, Ireland). The results are expressed as mean ± sd. Comparisons between and within groups were done with ANOVA.

The girls with FPP and SPP were compared for maternal age at menarche and mother’s final height; paternal age at first full shaving and father’s final height; age at appearance of the first secondary sexual signs; age, Tanner stage, bone age, and BMI at admission; and hormonal profile. Within the FPP group, girls with one affected family member were compared with girls with more than one affected family member. Familial pedigrees were assigned as maternally inherited, paternally inherited, both maternally and paternally inherited, or undetermined according to the sex of the individual who transmitted the trait. The latter subgroups were compared.

Results

The 156 children with true precocious puberty included 147 girls and nine boys; the female-to-male ratio was 16.3:1. Forty-three children (27.5%) with true precocious puberty met the criteria for FPP, including 42 girls and one boy. An additional four patients with FPP were not admitted during the study period and were therefore included only in the segregation analysis and in characterization of familial cases. The data of the 46 girls with FPP were compared with the data of the 105 girls with SPP.

In two families of the sporadic group, consanguinity was reported; in one family, parents were first cousins, and in the other, they were remote cousins. No consanguinity was reported in any of the familial cases.

Characteristics of FPP

In 22 of the 46 girls (42 plus 4) with FPP (47.8%), a parent was also affected (18 mothers and 4 fathers), and in 17 of the 37 FPP cases (45.9%) in which three-generation information was available, a grandparent was also affected. Of the 46 girls with FPP, 16 (34.8%) had one family member with precocious puberty, 11 (23.9%) had two affected family members, 10 (21.7%) had three, four (8.7%) had four, three (6.5%) had five, one (2.1%) had six, and one had seven (Fig. 1). Forty-three (93.5%) patients had a first-degree relative with precocious puberty, 27 (58.7%) patients had both first- and second-degree relatives, and some also had third-degree relatives with precocious puberty. In 16 cases (34.8%), the affected relatives were of the same generation (siblings and cousins); in 16 (34.8%) cases, relatives of two generations were affected; in 12 cases (26.1%), three generations; and in two cases (4.3%), four generations. In 33 cases (72%), the affected relatives were exclusively females, and in 13 cases (28%), they were of both sexes.

Precocious puberty was maternally inherited in 21 families, paternally inherited in 10 families, both maternally and paternally inherited in four families, and undetermined in 11.

Within the study group, there was no statistically significant difference for any of the parameters examined between the children who had one family member with precocious puberty and those who had more than one. Neither did we find a statistically significant difference between girls in whom inheritance was maternal and girls in whom inheritance was paternal.

Comparison of the data between the FPP and SPP groups is shown in Table 1. Information regarding maternal age at menarche was available for all mothers in the familial group and for 103 of 105 (98%) in the sporadic group; and information regarding paternal age at shaving was available for 34 of 46 fathers (73.9%) in the familial group and 63 of 105 (60%) in the sporadic group. Height measurements were available in all mothers in the familial group and in 104 of 105 (105) mothers in the sporadic group; height measurements were available in 42 of 46 fathers in the familial group and in 100 of 105 fathers in the sporadic group. Maternal age at menarche was significantly lower in the familial group than in the sporadic group (mean, 11.47 ± 1.96 yr vs. 12.66 ± 1.18 yr; P < 0.001). This finding held true even when the mothers with precocious puberty were excluded. However, the difference was not statistically significant and could be due to higher prevalence of mothers who had their menarche between the ages of 10 and 11 yr in the familial group (25.8%), after the above exclusion, compared with the sporadic group (9.7%; P = 0.03) (Fig. 2).

At presentation, 26 of 46 patients (56.5%) in the FPP group were in Tanner stage 2 compared with 82 of 105 (78.1%) in the SPP group (P = 0.006) (Fig. 3); corresponding rates for Tanner stage 3 were 32.6 and 20.9%, respectively. Two patients in the FPP group and one in the SPP group were in Tanner stage 4 at admission, and three patients with FPP and none in the SPP group were in Tanner stage 5. The between-group difference in the number of patients presenting with Tanner stage 4 or 5 was statistically significant (P = 0.003).

Paternal height was lower in the FPP than in the SPP group.
FIG. 1. Pedigrees of 46 girls with precocious puberty. Individuals with blackened symbols met criteria of precocious puberty. Gray symbols denote early puberty. Brothers younger than 9 yr and sisters younger than 8 yr are marked with an asterisk. Individuals for whom information regarding puberty was not available are indicated by a question mark.
In the present study, we assessed the familial pattern of central precocious puberty. We included all data obtained from three generations, excluding young siblings, to minimize inaccuracies due to recall bias in third-generation relatives. We found that the segregation ratio was higher for females than males, assuming incomplete penetrance, especially in males. To minimize inaccuracies due to recall bias in third-generation relatives, we used only two generations for segregation analysis. However, in 22 of the 46 cases of FPP (47.8%), a parent was also affected (18 mothers and 4 fathers), and in 17 of the 37 familial cases in which three-generation information was available, a grandparent was also affected. This high prevalence among parents and grandparents supports an autosomal dominant inheritance. In familial pedigrees 7 and 18, the disorder seemed to be inherited from father to son, which negates an X-linked dominant inheritance in these cases. Thus, the familial cases in most pedigrees suggest an autosomal dominant inheritance with reduced penetrance. This, however, does not exclude genetic heterogeneity of the disorder.

It is well established that central idiopathic precocious puberty is 10 times more common in females than in males (20). Normal puberty is also different between the sexes in time of onset, pace, and order of events, as is the cyclic pattern of GnRH and gonadotropin secretion. The strong female preponderance of idiopathic precocious puberty may indicate that the regulatory centers activating the hypothalamic GnRH secretion are more susceptible to disturbances.
in girls than in boys. The reason for the striking sex difference in the prevalence of idiopathic precocious puberty remains to be elucidated, but it could explain the deviation from the expected 50:50 ratio in autosomal dominant inheritance of siblings affected and of parental side of inheritance. This sex difference could also explain the difference in penetrance between females (73%) and males (42%). We therefore suggest that penetrance is sex-dependent.

The sporadic cases may represent another entity (e.g., exposure to estrogen-containing substances not disclosed by the medical history) or other modes of inheritance: autosomal recessive, in which there is rarely a family history; or new dominant mutations. This may be supported by the existence of two families in the sporadic group for whom consanguinity was reported. Our definition of familial cases was based on the existence of more than one affected family member either in the proband generation or in the pedigree.

The high female-to-male ratio in the SPP group (16.3:1) is similar to that reported in the literature (10:1 in most series) (21). However, the ratio tends to be higher in FPP, perhaps indicating a delayed medical attention in boys with a familial history.

We found a 27.5% frequency of FPP among patients diagnosed at our institute with central precocious puberty. This rate is higher than expected on the basis of the 5.2% rate of familial cases reported by Rohn and Rousonelos (3). The discrepancy might be explained by the number of patients studied (58 vs. 156 here), the methods used to evaluate the patients, and the fact that patients referred to a tertiary center might be a selective population. The percentage of familial cases might actually be higher than 27.5% because some patients defined as sporadic may have the genetic background but still do not meet the criteria of a familial case. Therefore, if families in which the proband is the last-born are considered normal in a family in which other members had pubertal signs at the same age.

FIG. 3. Tanner stage at presentation of the FPP group (A) and the control group (B); P = 0.006 for Tanner stage 2, P = not significant (NS) for Tanner stage 3, P = 0.003 for combined Tanner stages 4 and 5.

Data regarding age at pubertal changes for the parents' generation was based on parental reports. Recalled information has been found to be valuable because even decades after the event, 75–90% of women remember their age of menarche, and 50% of men remember the timing of their pubertal growth spurt, within 1 yr (25–29). Information regarding age at menarche of grandmothers is probably less accurate. Moreover, menarche before age 10 yr (girls) or shaving before age 13 yr (boys) does not necessarily indicate real precocious puberty. Unfortunately, no better tools for obtaining this information are available today.

Fathers in the FPP group were on the average 4 cm shorter than fathers in the SPP group; this difference was statistically significant. This finding might represent a compromised final height due to precocious or early puberty in some of the fathers. We cannot prove this assumption, because some of the details regarding puberty were missing for the fathers, and others were not as accurate as those for the mothers. Nevertheless, this is further supported by the increase in paternal height difference when patients whose mothers had precocious puberty were excluded. The increased height difference also supports our assumption of autosomal dominant inheritance. In autosomal dominant inheritance, usually only one parent is affected. Therefore, if families in which the trait was inherited from the mother are excluded, compromised final paternal height in the remaining families may imply that the children probably inherited the FPP from their fathers.

In conclusion, we suggest that familial central precocious puberty is autosomal dominantly inherited with reduced, sex-dependent penetrance. Larger, prospective studies are needed to confirm our findings. Molecular analysis of familial cases may shed light on the physiological mechanisms of puberty and contribute to the understanding of the pathogenesis of precocious puberty.

Although our study does not reflect the prevalence of FPP in the general population, the high prevalence of familial cases in our tertiary care center suggests that when a child is diagnosed with precocious puberty, a careful, detailed inquiry of the extended family regarding precocious puberty should be sought. Parents should be notified of the possibility of the disorder occurring in their other children, not
only in familial cases, but even when no family history exists because penetrance is reduced. Moreover, we recommend close follow-up of growth and pubertal changes in the younger siblings.

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