Premature Pubarche before One Year of Age: Distinguishing between Mini-Puberty Variants and Precocious Puberty

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Source of support: Departmental sources

Background: The aim of this study was to facilitate the distinction between the benign “mini-puberty of early infancy” and precocious puberty (PP).

Material/Methods: We compared 59 patients (21 boys and 38 girls) seen for pubic hair development before one year of age diagnosed as mini-puberty to 13 patients (2 boys) in whom pubertal development before one year revealed a PP.

Results: The boys with mini-puberty presented with pubic hair development and prepubertal testicular volume, with low plasma testosterone concentrations. Their gonadotropin responses to gonadotropin releasing hormone (GnRH) test showed predominant luteinising hormone increase in 9/13. The girls presented with pubic hair development that was accompanied by breast development in 47% of cases, with low plasma estradiol concentrations. Their gonadotropin responses showed predominant follicle-stimulating hormone increase in the 17 evaluated.

The patients with PP had organic central PP (5 hypothalamic hamartoma) or idiopathic central PP (n=6), or peripheral PP (one ovarian tumor and one congenital adrenal hyperplasia). The diagnosis was challenging only in 3 girls with idiopathic central PP presenting with prepubertal plasma estradiol concentrations and responses to GnRH test.

Conclusions: The diagnosis of PP was easily determined based on the clinical presentation and the pubertal concentrations of testosterone in boys or of estradiol in girls, as was the diagnosis of central or peripheral origin of PP based on gonadotropin response to the GnRH test. Once PP is excluded, these patients need careful follow-up and physician consultation is needed if clinical pubertal signs progress.

MeSH Keywords: Infant • Puberty • Puberty, Precocious

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/893139
Background

Precocious puberty (PP) is defined by the development of sexual characteristics before the age of 8 years in girls and 9 years in boys [1]. It is usually due to the premature activation of the hypothalamic-pituitary-gonadal axis, which is known as central PP (CPP). In girls, CPP is predominantly idiopathic, while in boys it is due to hypothalamic-pituitary lesions in the majority of cases [2].

The development of sexual characteristics before one year of age is very rare, except for breast development in girls, which is usually diagnosed as premature thelarche (PT). The characteristics of PT typically make it easy to distinguish from PP: isolated breast development before 2 years of age without accompanying pubic or axillary hair development or growth rate acceleration. However, PT has been reported to be followed by CPP in 13 to 18.4% of cases [3–5]. Identifying patients who will subsequently develop CPP among girls with PT is challenging [6]. This finding has led to the hypothesis that PT and CPP may represent different positions along a continuum of hypothalamic gonadotropin releasing hormone (GnRH) neuron activation [7].

The development of pubic and/or axillary hair before one year of age in both sexes, accompanied by breast development in some girls, complicates the diagnosis between “mini-puberty of early infancy” and PP. To the best of our knowledge, there are no reported data with large numbers of cases of children younger than one year old with pubertal development, except for cases of children with PT, and 11 cases reported by Nebesio and Eugster of children (6 boys and 5 girls) with transient pubic hair development [8].

Objective: We analyzed data from 59 consecutive patients seen over 8 years by a senior pediatric endocrinologist for pubertal development before one year of age who were diagnosed as mini-puberty of early infancy and PP. To the best of our knowledge, there are no reported data with large numbers of cases of children younger than one year old with pubertal development, except for cases of children with PT, and 11 cases reported by Nebesio and Eugster of children (6 boys and 5 girls) with transient pubic hair development [8].

Material and Methods

Ethics statement

Signed informed consent for the evaluations was obtained from the children’s parents and included in the children’s hospital medical record. All clinical investigations were conducted according to the principals expressed in the Declaration of Helsinki. The Ethical Review Committee (Comité de Protection des Personnes, Ile de France III) specifically approved this study, and stated that “This study appears to be in accordance with the scientific principles generally accepted and to the ethical standards of research. The study was lead in the respect of the French law and regulation”.

Patients

This single-center retrospective cohort study analyzed the data of 59 patients (21 boys and 38 girls) seen for pubic hair development before one year of age and diagnosed with mini-puberty between May 2004 and May 2012 by a senior pediatric endocrinologist (R Brauner) in a university pediatric hospital. The data from these patients were compared to data from 13 patients (2 boys and 11 girls) seen by the same physician for pubertal development including pubic hair development beginning at the same age and diagnosed with PP between 1982 and 2013. Some of the data from these patients had previously been included in larger studies that included patients seen for PP by the same physician [9–12].

Girls seen during the same time period for isolated PT were not included. Instead, they were evaluated once to confirm the diagnosis of PT, and their physician and parents were asked to redirect them to us if their breast development increased, if pubic hair development occurred, or if growth acceleration was noted before 8 years of age.

Methods

During the study period, local protocol required the systematic prescription of an adrenocorticotropin (ACTH) test for all patients seen for pubic hair onset before age 8 years in girls and age 9 years in boys. Patients younger than one year were therefore identified from the list of patients evaluated by an ACTH and/or a GnRH stimulation test over the 8 years of the study. Among 21 boys with mini-puberty, in 13 boys, the ACTH test was followed by a GnRH stimulation test in a single sequence, even if testicular volume was prepubertal, with the hypothesis that pubic hair development may be the first sign of CPP. Girls were evaluated with an ACTH test followed by a GnRH stimulation test if pubic hair development was accompanied by breast development (n=17). The following additional evaluations were performed and were normal: the plasma concentrations of α-feto protein and β human chorionic gonadotropin were measured in 13 boys and 13 girls, pelvic ultrasound evaluation was performed in 4 girls, and magnetic resonance imaging was conducted in 3 boys because of a pubertal response to the GnRH stimulation test.

The initial evaluation included the determination of height, weight, and pubertal stage. The ACTH test included measures...
of the plasma concentrations of 17-OH progesterone (17OHP) and cortisol in the basal state and one hour after an intramuscular injection of 0.25 mg of Synacthen®. The hypothalamic-pituitary-gonadal axis was evaluated by measuring basal luteinizing hormone (LH) and follicle-stimulating hormone (FSH), LH and FSH peaks at 30, 60 and 90 min after GnRH (100 μg/m²) stimulation, and basal plasma concentrations of testosterone in boys and estradiol in girls. LH and FSH were measured by two-site monoclonal immunoradiometric assays (LH-Coatria and FSH-Coatria; bioMerieux, SA, Marcy-l’Etoile, France). Estradiol and total testosterone were extracted with ether and measured by radioimmunoassay (Estradiol-2; Sorin Biomedica, Antony, France and Cis Bio, Gif sur Yvette, France). Each new assay for a given hormone was consistently cross-correlated with the previous method to ensure that the results were comparable throughout the study period. Prepubertal children had plasma concentrations below 0.15 ng/mL for testosterone in boys and below 14 pg/mL for estradiol (45th percentile) in girls.

Height, growth rate and body mass index (BMI, weight in kg/height in m)² were expressed relative to the standard deviation (SD) for the chronological age [14,15]. The pubertal stage was rated according to the standards of Marshall and Tanner [16,17]. Intrauterine growth retardation (IUGR) was defined as a weight or height at birth below the 3rd percentile for gestational age [18]. Basal concentrations of 17OHP <2 ng/mL and delta4-androstenedione (D4A) <0.95 ng/mL were considered normal [13]. Plasma steroid concentrations were compared to those reported by Lashansky et al. [19]. An LH/FSH peak ratio after the GnRH stimulation test >0.66 in girls and >2 in boys was considered to be pubertal [20].

The data are expressed as the mean ±SD.

Results

Boys with mini-puberty

Only case 1 had IUGR, and cases 16 and 21 were born prematurely (<37 weeks gestation) (Table 1). The interval between the onset of pubic hair development and the evaluation was 3.2±2.4 months. Pubic hair development was Tanner stage P2 in all but case 10, which was Tanner stage P3, and testicular volume was lower than 3 mL in all cases. Only one case (case 16) was not evaluated by an ACTH test because the basal plasma concentrations of the adrenal hormones evaluated by his physician were normal. One boy (case 3) had increased basal and stimulated plasma concentrations of 17OHP, leading to a second test showing normal concentrations and to genetic analysis of the 21-hydroxylase gene, which showed heterozygosity. The response to the GnRH stimulation test was pubertal in 9 boys and prepubertal in 4 boys. Their plasma testosterone concentrations were low at the first and/or second evaluation performed over the following 3 months. In case 10, there was no second biological evaluation or MRI, but the pubic hair development had not progressed 3 years later.

Girls with mini-puberty

Cases 16 and 36 had IUGR, and 7 girls were born prematurely (cases 10–13, 16, 26 and 37) (Table 2). The interval between the onset of pubic hair and/or breast development and the evaluation was 3.4±4.0 months. Pubic hair development was Tanner stage P2 in all but cases 5, 8, 10 and 18, which were Tanner stage P3. A total of 18/38 (47%) girls had breast development associated with pubic hair development, and one had menstruations in the neonatal period. Height was less than –2 SDs in 2 patients (cases 15 and 35) and greater than 2 SDs in 3 patients (cases 5, 12 and 36). Additional evaluations performed in the 2 girls with short stature showed no abnormality. BMI was below –2 SDs in one patient and over 2 SDs in two patients. Two girls (cases 4 and 38) had increased basal plasma concentrations of 17OHP, and one of these had an increased response to the ACTH test, but genetic analyses of the 21-hydroxylase gene were normal. All plasma testosterone concentrations were undetectable or very low. The response to the GnRH stimulation test was prepubertal in the 17 girls evaluated because of breast development or menstruation associated with pubic hair development. Plasma estradiol concentrations were below or just above (cases 22 and 31) the prepubertal value in the 33 girls evaluated.

Patients with PP

Patients with PP had organic CPP (n=5) or idiopathic CPP (n=6) or peripheral PP (one ovarian tumor and one congenital adrenal hyperplasia) (Table 3). The interval between the onset of puberty and the evaluation was 9.4±9.7 months. One girl with hypothalamic hamartoma and the girl with granulosa tumor had menstruations.

Patients with organic CPP included 2 boys and 3 girls with hypothalamic hamartoma. All had pubertal concentrations of testosterone in boys and estradiol in girls, and a pubertal response to the GnRH stimulation test, except for case 5, whose LH/FSH peak ratio was 0.4 with a concomitant plasma estradiol concentration of 50 pg/mL.

Patients with idiopathic CPP included 6 girls. They presented with breast and pubic hair development. All but 2 cases (cases 9 and 10) had prepubertal gonadotropin responses to the GnRH stimulation test as well as prepubertal plasma estradiol concentrations, but breast development nonetheless progressed, leading to GnRH analog treatment in all but case 7. In 3 cases (cases 6–8), there was familial CPP.
One girl had a granulosa tumor of the ovary with significant clinical and biological signs of estradiol secretion. The girl with congenital adrenal hyperplasia had signs of hyperandrogenemia and a very high concentration of plasma basal 17OHP.

### Discussion

This is to our knowledge the first study specifically addressing the distinguishing features between the mini-puberty of the infant and various forms of PP in children presenting with premature pubarche prior to one year of age. Our findings are important because of the difficulties in predicting which children presenting with signs of sexual precocity in this age group go on to develop sustained pubertal development.

### Characteristics of the population with mini-puberty

We based our diagnoses on clinical presentation, prepubertal plasma concentrations of testosterone in boys and estradiol in girls.

| Case | Age at onset, mo | Height, SDS | BMI, SDS | ACTH, Basal, pg/mL | Peak, ng/mL | 17OHP, ng/mL | DOC, ng/mL | LH, IU/L | FSH, IU/L | LH/FSH peaks ratio | Testosterone (1st), ng/mL | Testosterone (2nd), ng/mL |
|------|-----------------|-------------|----------|-------------------|-------------|-------------|-------------|----------|----------|---------------------|--------------------------|--------------------------|
| 1    | 0               | -2.2        | 1.1      | 16                | 0.9         | 4.7         | 0.2         | NA       | 2.3      | 2.2                | 1.0                      | <0.05                    |
| 2    | 0               | -1.1        | 1.1      | 13                | 0.9         | 3.3         | NA          | 161.0    | 12.0     | 3.1                | 3.9                      | 0.14                     |
| 3    | 1               | 0.3         | 1.0      | 24                | 3.4         | 13.7        | 0.3         | 19.0     | 7.0      | 3.6                | 1.9                      | <0.05                    |
| 4    | 2               | 0.0         | NA       | 21                | 0.6         | 2.7         | NA          | 311.0    | NA       | NA                 | NA                      | <0.05                    |
| 5    | 3               | -0.4        | -1.8     | NA                | 0.6         | 3.0         | 0.2         | 757.0    | 12.5     | 5.2                | 2.4                      | 0.03                     |
| 6    | 3               | 3.3         | 1.5      | -0.9              | 53          | 0.7         | 1.0         | 0.3      | 987.0    | 8.2                | 1.4                      | 5.9                      |
| 7    | 2               | 0.9         | 0.8      | 15                | 1.4         | 8.0         | 0.2         | 19.0     | NA       | NA                 | NA                      | <0.05                    |
| 8    | 4               | 5.5         | 1.0      | 0.5               | 31          | 0.7         | 1.6         | 0.4      | 907.0    | 7.1                | 1.8                      | 3.9                      |
| 9    | 4               | 7           | 0.5      | -1.5              | 14          | 0.7         | 3.8         | 0.1      | 35.0     | 20.5               | 1.3                      | 15.8                     |
| 10   | 4               | 8           | 0.1      | -0.3              | 0.2         | 15          | 0.4         | 2.4      | 0.2      | NA                 | NA                      | <0.05                    |
| 11   | 4               | 6           | -0.3     | 1.0               | 2.0         | 0.5         | 2.3         | 0.2      | 521.0    | NA                 | NA                      | 0.22                     |
| 12   | 4               | 6           | -1.2     | -1.2              | 26          | 0.2         | 2.4         | 0.1      | 388.0    | NA                 | NA                      | <0.05                    |
| 13   | 4               | 8           | -0.7     | 1.6               | 9.0         | 2.2         | 4.3         | NA       | NA       | 6.1                | 2.6                      | 2.3                      |
| 14   | 6               | 8           | -0.7     | 1.6               | 9.0         | 2.2         | 4.3         | NA       | NA       | 6.1                | 2.6                      | 2.3                      |
| 15   | 6               | 7           | 0.9      | -0.2              | 23          | 0.3         | 1.6         | NA       | 1500.0   | 9.1                | 3.5                      | 2.6                      |
| 16   | 6               | 8           | -0.3     | -1.7              | 16          | 0.3         | NA          | 0.1      | 12.5     | 1.9                | 6.6                      |
| 17   | 6               | 7           | 0.9      | -1.4              | 16          | 0.4         | 3.1         | 0.2      | 19.0     | NA                 | NA                      | 0.12                     |
| 18   | 6               | 6           | -1.0     | 0.1               | 33          | 0.4         | 1.1         | 0.3      | 92.0     | NA                 | NA                      | 0.06                     |
| 19   | 8               | 10          | -0.1     | 0.1               | 27          | 0.8         | 1.1         | 0.2      | 14.0     | 2.9                | 3.4                      | 0.9                      |
| 20   | 8               | 9.5         | -0.1     | 1.7               | 51          | 0.1         | 1.2         | 0.1      | 2.2      | 1.2                | 1.8                      |
| 21   | 11              | 14          | 0.8      | 1.9               | 17          | 0.2         | 1.0         | 0.1      | 96.0     | NA                 | NA                      | <0.05                    |
| Mean | 4.4             | 7.6         | 0.1      | 0.6               | 27.2        | 0.8         | 3.2         | 0.2      | 388.4    | 8.4                | 2.7                      | 3.9                      |
| SD   | 2.7             | 2.2         | 0.9      | 1.2               | 18.5        | 0.8         | 3.0         | 0.1      | 456.8    | 5.1                | 1.2                      | 3.9                      |

3 had normal cerebral MRI (cases 3, 7 and 16). Normal values: ACTH (14–45) pg/mL, basal 17OHP (0.1–2.0) ng/mL, peak 17OHP <10 ng/mL, D4A (0.06–0.54) ng/mL, DOC (deoxycorticosterone) (70–520) pg/mL.
Table 2. Characteristics of the girls seen for mini-puberty.

| Case | Age at onset, mo | Age at evaluation, mo | Pubertal stage | Height, SDS | BMI, SDS | ACTH, basal, pg/mL | ACTH, peak, pg/mL | Testosterone, ng/mL | D4A, ng/mL | DOC, ng/mL | LH, IU/L | FSH, IU/L | LH/FSH peaks ratio | Estradiol, pg/mL |
|------|-----------------|----------------------|----------------|-------------|-----------|------------------|------------------|-------------------|-------------|------------|-----------|------------|------------------|-----------------|
| 1    | 0               | 15                   | P2M            | 1.3         | 2.2       | 32               | 0.6              | NA                | NA          | 0.04       | NA        | 6.2       | 35.0             | 0.2             | 2               |
| 2    | 0               | 11                   | P2B1           | 0.5         | -0.5      | 11               | 0.5              | 2.6               | <0.02       | 0.1        | NA        | NA        | NA             | NA              | NA              |
| 3    | 1               | 8                    | P2B1           | 0.7         | -0.5      | 20               | 0.3              | 2.7               | <0.05       | 0.1        | NA        | NA        | NA             | NA              | 4               |
| 4    | 1               | 10                   | P2B1           | 1.4         | -0.4      | 70               | 2.5              | 4.3               | 0.04        | 0.3        | 633       | NA        | NA             | NA              | 4               |
| 5    | 1               | 12                   | P3B1           | 2.3         | 0.3       | 22               | 0.4              | 2.4               | 0.03        | 0.3        | 59        | NA        | NA             | NA              | 3               |
| 6    | 2               | 7                    | P2B1           | -1.0        | 1.5       | 25               | 0.7              | 2.4               | <0.02       | 0.1        | NA        | NA        | NA             | NA              | 6               |
| 7    | 2               | 8                    | P2B2           | 1.9         | -0.9      | 22               | 0.4              | 2.6               | <0.02       | <0.02      | 60        | NA        | NA             | NA              | 10              |
| 8    | 3               | 7                    | P3B3           | 0.6         | 0.4       | 25               | 0.7              | NA                | 0.08        | NA         | 526       | 33        | 27.0             | 0.1             | 7               |
| 9    | 3               | 8                    | P2B1           | -0.1        | 0.1      | 13               | 0.6              | 3.3               | <0.02       | 0.3        | 657       | NA        | NA             | NA              | 7               |
| 10   | 4               | 7                    | P3B2           | -0.3        | 0.7      | 36               | 1.7              | 4.0               | 0.03        | 0.4        | 230       | 34        | 35.0             | 0.1             | 2               |
| 11   | 4               | 6                    | P2B3           | -0.5        | -0.6     | 18               | 0.2              | NA                | <0.02       | NA         | 3.0       | 16.5      | 0.2             | <2              | 2               |
| 12   | 4               | 4                    | P2B2           | 2.5         | -0.2     | 7                | 0.3              | 3.3               | <0.02       | 0.3        | 334       | 15        | 11.0             | 0.3             | 3               |
| 13   | 4               | 6                    | P2B2           | -1.0        | -2.0     | 52               | 1.3              | 1.7               | <0.02       | NA         | 1397      | 5.4       | 44.5             | 0.1             | 4               |
| 14   | 5               | 7                    | P2B1           | 1.2         | -1.4     | 24               | 1.4              | 6.0               | <0.02       | 0.2        | 284       | NA        | NA             | NA              | NA              |
| 15   | 5               | 8                    | P2B2           | -2.7        | -2.1     | 82               | 0.4              | 2.1               | <0.02       | 0.3        | 35        | 28.0      | 0.1             | 5               | 5               |
| 16   | 6               | 6                    | P2B2           | 1.4         | 0.5      | 57               | 1.2              | 5.1               | <0.05       | 0.2        | 60        | NA        | NA             | NA              | 14              |
| 17   | 6               | 7                    | P2B1           | 0.6         | -0.3     | 34               | 1.4              | 4.0               | <0.05       | 0.2        | 28        | NA        | NA             | NA              | NA              |
| 18   | 6               | 8                    | P3B1           | -0.1        | -0.6     | 18               | 1.9              | 6.5               | 0.06        | 0.5        | 19        | NA        | NA             | NA              | 5               |
| 19   | 6               | 1                    | P2B1           | 0.1         | 0.0      | 32               | 0.6              | 2.5               | <0.02       | 0.2        | 19        | NA        | NA             | NA              | 7               |
| 20   | 6               | 14                   | P2B3           | 1.7         | -0.6     | 16               | 0.4              | 1.7               | <0.02       | 0.2        | 19        | NA        | NA             | NA              | 5               |
| 21   | 6               | 10                   | P2B2           | 1.6         | 0.5      | 12               | 0.5              | 3.9               | <0.02       | 0.3        | 177       | NA        | NA             | NA              | <2              |
| 22   | 6               | 9                    | P2B1           | 1.7         | -0.6     | 16               | 0.4              | 1.7               | <0.02       | 0.3        | 19        | NA        | NA             | NA              | 15              |
| 23   | 6               | 7                    | P2B2           | 1.4         | -1.5     | 13               | 0.1              | NA                | <0.02       | 0.3        | NA        | NA        | NA             | NA              | 11              |
| 24   | 7               | 7                    | P2B2           | 0.7         | -0.9     | NA               | 0.4              | 4.0               | <0.05       | 0.1        | 78        | 6.1       | 30.5             | 0.2             | 4               |
| 25   | 7               | 7                    | P2B2           | 1.6         | -1.0     | 8                | 0.2              | 1.9               | <0.05       | 0.1        | 61        | 28.5      | 0.2             | 10              | 4               |
| 26   | 7               | 9                    | P2B1           | 0.4         | -0.6     | 22               | 1.6              | 6.2               | 0.02        | 0.3        | 43        | NA        | NA             | NA              | 3               |
| 27   | 7               | 9                    | P2B2           | 0.5         | -0.5     | 15               | 0.2              | NA                | <0.02       | NA         | 91        | 30        | 15.0             | 0.2             | <2              |
| 28   | 7               | 9                    | P2B2           | -0.7        | -1.0     | 16               | 0.8              | NA                | <0.02       | NA         | 4.1       | 38.0      | 0.1             | 4               |                 |
| 29   | 8               | 8                    | P2B1           | 0.5         | 0.6      | 40               | 2.1              | 3.9               | <0.05       | 0.3        | 19        | NA        | NA             | NA              | 4               |
| 30   | 8               | 18                   | P2B1           | -0.2        | -0.5     | 15               | 0.4              | 2.3               | <0.05       | 0.2        | 112       | NA        | NA             | NA              | NA              |
| 31   | 8               | 10                   | P2B1           | -0.8        | -0.6     | 6                | 0.7              | 7.1               | 0.03        | 0.2        | 60        | NA        | NA             | NA              | 18              |
| 32   | 8               | 9                    | P2B2           | -0.5        | -0.4     | 16               | 0.4              | 4.0               | <0.02       | NA         | <60       | 4.9       | 30.5             | 0.2             | NA              |
The frequency of IUGR, the distributions of height and BMI, and the ACTH stimulation test responses were similar to the normal data for age, but the frequency of prematurity in girls was greater (18.4% vs. 7.4% in the general French population in 2010). All boys had prepubertal testicular volume, but the gonadotropin responses to the GnRH stimulation test were pubertal in the majority of those evaluated. In

| Case | Sex | Diagnosis      | Age at onset, mo | Age at evaluation, mo | Pubertal stage | Height, SDS | BMI, SDS | ACTH, pg/mL | basal, ng/mL | peak, ng/mL | Testosterone, ng/mL | D4A, ng/mL | DOC, pg/mL | LH, IU/L | FSH, IU/L | LH/FSH peaks ratio | Estradiol, pg/mL |
|------|-----|----------------|------------------|-----------------------|----------------|------------|----------|-------------|--------------|-------------|---------------------|-------------|------------|----------|-----------|---------------------|-----------------|
| 52   | F   | Hamartoma      | 10               | 15                    | P2B1          | –2.4       | 0.9      | 17          | 1.0          | 5.0        | <0.02               | NA          | 8.6        | 52.5     | 0.1       | 2                   | –               |
| 53   | F   | Hamartoma      | 11               | 16                    | P2B2          | 0.8        | 0.5      | 16          | 0.9          | 4.3        | <0.05               | 0.6         | 19         | 3.3      | 34.0      | 0.1                 | 10              |
| 54   | F   | Hamartoma      | 6                | 12                    | P2B3M         | –0.73      | 18       | 41          | 3.7          | 10.5       | 0.06                | 3.1         | 52         | 0.1      | 3         | 0.01                | 3               |
| 55   | M   | Hamartoma      | 9                | 10                    | P2B2          | 2.0        | 0.7      | 19          | 0.9          | 3.9        | –                   | –           | 987        | NA       | NA        | NA                  | –               |
| 56   | F   | Hamartoma      | 10               | 13                    | P2B1          | –2.4       | 2.9      | 41          | 3.7          | 10.5       | 0.05                | 3.1         | 52         | 0.1      | 3         | 0.01                | 3               |
| 57   | M   | Hamartoma      | 9                | 12                    | P2B3          | 1.9        | –        | –           | –            | 10         | 2.5                 | 24          | NA         | NA       | –         | 0.1                 | –               |
| 58   | F   | Hamartoma      | 8                | 11                    | P2B2          | –0.84      | –        | –           | –            | 10         | 3.1                 | 28          | 0.1        | 0.11     | 0.11      | 0.01                | –               |
| 59   | F   | Hamartoma      | 12               | 15                    | P2B2          | –0.6       | –        | 17          | 0.2          | 4.4        | –                   | –           | 34         | 23.3     | 0.4       | –                   | –               |
| 60   | F   | Hamartoma      | 6                | 9                     | P2B3          | 1.9        | –        | 9           | 2.6          | 17         | 0.15                | –           | 27         | 2        | 0.2       | –                   | –               |
| 61   | F   | Hamartoma      | 12               | 13                    | P3B2          | 0.14       | –        | 50          | 0.2          | 52         | 27                 | 2           | –          | –        | –         | –                   | –               |
| 62   | F   | Hamartoma      | 6                | 7                     | P3B2          | 0.2        | –        | 100         | 0.5          | 0.2        | –                   | –           | –          | –        | –         | –                   | –               |
| 63   | M   | Hamartoma      | 10               | 8                     | P2B2          | –0.16      | –        | 9           | 2.5          | 17         | 0.15                | –           | 27         | 2        | –         | –                   | –               |
| 64   | F   | Hamartoma      | 6                | 7                     | P3B3M         | 2          | 1.44     | 178         | 0.5          | 0.2        | –                   | –           | –          | –        | –         | –                   | –               |

CAH – congenital adrenal hyperplasia. Basal 17OHP 223 ng/mL in case 13. 3 cases of Idiopathic CPP were familial forms (case 6–8).

Table 3. Characteristics of the patients seen for PP before one year of age.
girls with breast and pubic hair development, plasma estradiol concentrations were low, and predominant FSH increases were observed after the GnRH stimulation test.

Premature pubarche is rare before the age of 2 years and may be the result of hypothalamic-pituitary activation rather than adrenal activation. In a previous study, we found that among 216 children seen for premature pubarche between September 1992 and September 2001, only 21 girls and one boy were younger than 2 years at onset [21]. The incidence of obesity was significantly lower in these patients than in the older patients. They had above-normal plasma D4A and dehydroepiandrosterone sulfate concentrations for their sex and age, but these concentrations were lower than those expected in Tanner stage 2. We concluded that premature pubarche at this age may not be simply a “premature adrenarche”, and the gonads may be involved in the development of pubic hair. Thus, the transient surge in GnRH was associated with pubertal concentrations of LH (higher in males) and FSH (higher in females), but the amplitude and duration of this reactivation differed between the two sexes [22]. Forest et al. [23] showed that after the end of the first postnatal week in normal boys, plasma testosterone rises progressively, peaking around the second month, before decreasing to prepubertal values near 6 months. Gendrel et al. [24] showed a highly significant positive correlation between LH and testosterone plasma concentrations in samples collected from day 7 to day 180 of life in boys, suggesting that the postnatal rise of testosterone is under pituitary control.

Characteristics of the population with PP

CPP before the age of one year is exceedingly rare, even among patients with organic forms related to brain tumors and/or malformations. Chaussain et al. [25] reported that among the 10 boys with CPP (only one idiopathic aged 10.5 yr), the 3 younger than one year included two boys with tumors of the 3rd ventricle and one with ventricular dilatation; all had pubertal concentrations of testosterone. Rivaolora et al. [26] reported that among the 30 patients with CPP and organic central lesions, 3 were younger than one year and had hypothalamic hamartoma, germinoma or suprasellar arachnoid cyst. Zuniga et al. [27] reported that CPP due to hypothalamic hamartoma begins before 3 years of age in 84% of cases. Cacciari et al. [28] showed that all girls with pubertal signs before 2 years of age and 80% with early menarche due to CPP had a suspected hamartoma.

Only 2.2% of our 493 girls with idiopathic CPP were younger than 3 years at the onset of puberty [11]. Diagnostic challenges remain giving the similarities in the testing results between the patients who developed idiopathic CPP and those with mini-puberty [6]. Among the 3 girls with granulosa tumors seen during the study period, one was younger than one year and was included in the present study, and the 2 others were older (and had been included in [29], which reported that 17/27 prepubertal girls with ovarian granulosa cell tumors presented with PP). Cameron et al. [30] reported PP due to a granulosa cell tumor in a 7-month-old female and collected 4 reported cases aged less than one year. Heller et al. [31] reported 4 girls aged 3 months to 2.2 yrs (2 girls were younger than 1 yr) with recurrent vaginal bleeding in the absence of other signs of precocious sexual development (such as breast development). The authors suggested that increased sensitivity of the endometrium to estradiol might be a cause of vaginal bleeding among these girls. One girl diagnosed at 10 months with a simple virilizing form (Prader 2) of congenital adrenal hyperplasia presented with pubic hair development, while her brother had the salt wasting form, which was diagnosed by a neonatal screening [12]. In a previous study performed to distinguish late-onset congenital adrenal hyperplasia from premature adrenarche, we identified three plasma predictors of congenital adrenal hyperplasia in patients presenting with pubic hair development [13].

There were no patients in this study where PP revealed McCune-Albright syndrome, adrenal or testicular tumors. The patients seen with these diagnoses during the same period were all older than one year. They had increased basal plasma concentrations of testosterone in boys and estradiol in girls. The tumors were Leydig cell adenoma (one boy age 5 years) and corticosurrenaloma (2 boys: one published in [32], and the other presented with pubic hair development and gynecomastia at 9 years). One boy with 11β-hydroxylase deficiency presented with pubic hair development at 1.2 years and a pubertal plasma testosterone concentration of 2 ng/ml at 2 years. Among 89 girls with PP due to McCune Albright syndrome including our patients [33], 13 were younger than one year, and among them, 7 had bone and/or skin lesions associated with PP, while 6 had isolated PP at presentation.

Diagnosis of PP versus mini-puberty

The presence of elevated testosterone concentrations in boys and of elevated estradiol concentrations in girls were the main features that distinguished infants presenting with premature pubarche who went on to develop PP from those with mini-puberty of infancy in our cohort. Diagnosis challenges remain giving the similarities in the testing results between patients who developed idiopathic CPP and those with mini-puberty in our cohort.

We suggest the following protocol for patients being evaluated for pubertal development before one year of age, excluding those with PT. In boys with bilateral increased testicular
volume and in girls with pubic hair and breast development, particularly if they are associated with increased cephalic diameter (suggesting a suprasellar arachnoid cyst), cutaneous lesions of neurofibromatosis or ophthalmic abnormality, a GnRH stimulation test should be performed without delay followed by an MRI if a central origin is confirmed. In the boys with prepubertal testicular volume and in the girls with isolated pubic hair development, the initial evaluation must include the levels of plasma ACTH, 17OHP (basal only or after an ACTH test) and testosterone. A GnRH stimulation test should be performed, and the concentration of plasma β human chorionic gonadotropin should be determined to identify germ cell tumors of the testes. If the testosterone concentration is increased. We performed both of these tests in a single evaluation because the cost was similar to one test alone.

**Study limitations**

This study has several limitations. First, it is retrospective. Second, the delay to exclude the occurrence of secondary PP in some patients with the benign form was insufficient, although PP requiring rapid treatment is easy to diagnose at first presentation. Third, the girls with PT were not analyzed, although we are confident that their parents and/or their physicians would have contacted us in case of evolution to PP. Similarly, despite a lack of follow-up with some patients, because all reports sent to the patients and to their physicians requested that we be contacted in case of progression to pubertal development, we are confident that there was no progression of pubertal development or an increase in the growth rate in the patients included in the study.

A prospective study would be required to test whether raised testosterone in boys and raised estradiol in girls is truly predictive of PP rather than of mini-puberty.

**Conclusions**

This study was the first of its kind to focus on patients with pubertal development before one year of age and on the criteria necessary to distinguish transient causes of PP - such as mini-puberty of early infancy – from PP requiring treatment without delay. Once PP is excluded, these patients need careful follow-up by their physician, and parents need written information educating them about the need for physician consultation if clinical pubertal signs progress or if their child’s growth rate is greater than normal for the age.

**Acknowledgements**

We thank Dr Véronique Tardy and Pr Yves Morel (Groupement hospitalier Est, Bron, 69677, France) for their collaboration in mutual participation of the CYP21 gene in 4 patients.

**Disclosure statement**

The authors have no conflicts of interest to disclose.

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