Precocious puberty in girls: early diagnosis of a slowly progressing variant

M FONTOURA, R BRAUNER, C PREVOT, AND R RAPPAPORT
Paediatric Endocrinology Unit and INSERM U30, Hôpital des Enfants Malades, Paris, France

SUMMARY An attempt was made to identify the less severe cases of precocious puberty and to describe their natural course. A group of 17 girls with precocious puberty and a bone age advance over chronological age of less than two years (group 1) was compared with a group of 19 patients with severe precocious puberty and bone age advance of two years or more (group 2). Mean (SEM) plasma oestradiol concentrations were 82 (30) pmol/l and 164 (21) pmol/l (p<0.05), vaginal maturation indexes were 16 (5) and 41 (4), and plasma somatomedin C concentrations were 1.0 (0.2) U/ml (n=8) and 2.1 (0.3) U/ml (n=16) in groups 1 and 2, respectively. The time between onset and diagnosis of secondary sexual characteristics was about one year in both groups. After two years' follow up the untreated patients in group 1 had maintained their predicted final height. These changes were in contrast to those observed at first examination in patients in group 2 who had a mean (SD) predicted final height of −1.3 (0.2) and a mean bone age advance of 3.0 (0.2) years. These data show that bone age advance to chronological age, and plasma somatomedin C concentrations measured at initial evaluation are helpful in identifying less severe and potentially slow progressing forms of central precocious puberty.

Children with central precocious puberty have a premature increase in the secretion of sex hormones that leads to acceleration of their growth rate. At the same time excessive progression of bone age may lead to short adult stature. The course of sexual precocity is variable, however, and in some cases normal growth continues with no reduction in predicted final height.1 This clinical heterogeneity may partly explain the difficulty that has been encountered in establishing the effectiveness of treatment with cyproterone acetate2 or medroxyprogesterone.3 More recently drugs such as luteinising hormone releasing hormone analogues have been shown to suppress gonadotrophin secretion and gonadal activity completely. Data from short term trials have already shown that there is an increase in the predicted final height.4–8 We have studied the spontaneous course of precocious puberty according to its initial presentation, to evaluate the early use of luteinising hormone releasing hormone analogues.

Patients and methods
Thirty six girls with idiopathic precocious puberty who had been regularly followed up in the paediatric endocrinology unit were assigned to this study. Informed consent was obtained from both them and their parents. The diagnostic criterion of precocious puberty was the occurrence of oestrogenic activity in association with the appearance of pubic hair before age of 8 years. Primary ovarian follicular cysts and adrenal diseases were ruled out. The plasma concentrations of β human chorionic gonadotrophin and α fetoprotein were normal. A computed tomogram of the head was carried out in all cases and was normal. No patient had previously received treatment for precocious puberty. Growth hormone secretion, evaluated by the arginine-insulin tolerance test, was normal.

Patients were arbitrarily classified into two groups (table 1) according to their bone age advance over chronological age at first examination: group 1 comprised patients in whom the advance was less than two years (cases 1–17) and group 2, patients in whom it was more than two years (cases 18–36). The bone age advance was selected as a discriminatory criterion because it had been used in this group to decide which patients were to receive treatment with the luteinising hormone releasing hormone...
### Table 1 Clinical and biological data for 36 girls with precocious puberty at time of first examination

<table>
<thead>
<tr>
<th>Case No</th>
<th>Chronological age (years)</th>
<th>Bone age (years)</th>
<th>Height (SD)</th>
<th>Pubertal stage&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Plasma oestradiol concentration (pmol/l)</th>
<th>Vaginal maturation index</th>
<th>Peak plasma luteinising hormone concentration (IU/l)</th>
<th>Peak follicle stimulating hormone concentration (IU/l)</th>
<th>Plasma somatomedin C/insulin like growth factor I concentration (U/ml)</th>
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<td>8-3</td>
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<tr>
<td><strong>Mean</strong> (SEM)</td>
<td>6-5 (0-4)</td>
<td>7-2 (0-4)</td>
<td>1-6 (0-3)</td>
<td>82 (30)</td>
<td>16 (5)</td>
<td>4-8 (1-4)</td>
<td>5-8 (0-9)</td>
<td>1-0 (0-2)</td>
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</tr>
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</table>

*p* Value compared with group 1: *p* < 0.2, *p* < 0.001, *p* < 0.1, *p* < 0.05, *p* < 0.01, *p* < 0.01, *p* < 0.01

In group 1 the spontaneous course of precocious puberty was followed up for a period of two years after the first examination and the patients received no treatment, with the consent of their parents. The patients in group 2 were treated with the analogue (Buserelin) after the first examination. The mean (SEM) chronological ages in the two groups at the time of first examination was 6-5 (0-4) years (range 2-8) and 7-3 (0-4) years (range 3-4-8-9), respectively. The mean (SEM) time intervals between the onset of sexual development and the first examina-
Puberty ratings were made according to Tanner's scale.\textsuperscript{9} Height changes were expressed as standard deviation scores taking the chronological age or the bone age as the reference measurement. Final heights were predicted according to the method Bayley and Pinneau\textsuperscript{10} using the bone age as assessed by Greulich and Pyle.\textsuperscript{11} Final predicted heights were expressed in relation to the mean normal adult height using standard deviation scores.\textsuperscript{12}

All patients were evaluated according to previously published methods for growth hormone secretion (arginine-insulin tolerance test\textsuperscript{13}) and basal serum values of oestradiol and somatomedin C/insulin like growth factor 1.\textsuperscript{14} The gonadal hypothalamic-pituitary axis was investigated by basal and luteinising hormone releasing hormone stimulated measurements of plasma luteinising hormone, and follicle stimulating hormone, as previously reported.\textsuperscript{15} The vaginal maturation index was evaluated by vaginal smear examination with an upper normal prepubertal value of 35.\textsuperscript{16}

The vaginal maturation index was not evaluated in cases 10, 11, 14, 15, and 16 at the time of their first examination. Cases 13 and 19 were not tested for luteinising hormone releasing hormone at their initial examination. All data are expressed as mean (SEM) and statistical comparisons were made by Student's paired t test on the same group, and by the unpaired t test between groups 1 and 2.

**Results**

**COMPARISON AT TIME OF DIAGNOSIS BETWEEN THE TWO GROUPS OF PATIENTS**

Tables 1 and 2 show the clinical presentation and biological data of the two groups. The distribution of the breast development stage in relation to the bone age advance is shown in the figure. The mean chronological ages at the first evaluation and the mean time from the onset of sexual development were similar in both groups. By definition the mean bone age advance (expressed as bone age minus chronological age) was significantly lower in patients in group 1 (0.7 (0.1) years) compared with group 2 (3 (0.2) years) (p<0.001). The mean height gains during the year before the initial evaluation were similar in both groups, 7.8 (0.8) cm and 8.5 (0.4) cm, respectively. Patients of group 1 were, however, slightly but not significantly shorter, with a mean (SD) height score for chronological age of 1.6 (0.3) above the normal mean compared with 2.4 (0.2) for patients of group 2 (p<0.05).

Patients in group 1 also had fewer clinical signs of excessive oestrogen production when first seen: vaginal bleeding in two cases (cases 3 and 4), breast development at Tanner's stage 2 in 14 patients, and stage 3 in one case (table 1). Pubic hair was present

<table>
<thead>
<tr>
<th>Case No</th>
<th>Bone age—chronological age (years)</th>
<th>Height (SD)</th>
<th>Height prediction (standard deviation score)</th>
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<tr>
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<td>0.0</td>
<td>1.5</td>
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</table>

Table 2. Spontaneous growth and bone maturation during the two years following the first examination in girls with precocious puberty and moderate oestrogen activity (group 1)
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Table 3  Plasma somatomedin C insulin like growth factor I concentrations and growth in girls with mild (group 1) or severe (group 2) precocious puberty at time of first examination. Values are expressed as mean (SEM)

<table>
<thead>
<tr>
<th>Group</th>
<th>No of subjects</th>
<th>Chronological age (years)</th>
<th>Bone age (years)</th>
<th>Bone age–chronological age (years)</th>
<th>Plasma somatomedin C/insulin like growth factor I concentration (pmol/l)</th>
<th>Plasma oestradiol concentration (pmol/l)</th>
<th>Height gain (cm/year)</th>
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<td>16</td>
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<td>42 (5)</td>
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<td>&lt;0-001</td>
<td>&lt;0-01</td>
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<td>&lt;0-001</td>
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</table>
years the mean advance of bone age over chronologi-
cal age was 1-1 (0-1) years (range 0-5-1-8). This was slightly but significantly higher than the value of
0-7 (0-1) years found at the time of diagnosis (p<0-05). The bone age advance had progressed by more
than one year in only four of 17 children (cases 4, 5, 15, and 16). It had remained unchanged or
decreased in six cases and progressed slightly in the
seven others. Height for chronological age, ex-
pressed by the standard deviation score, had a mean
(SD) value of 1-6 (0-4) compared with a similar
initial value of 1-6 (0-3). The mean (SD) final height
prediction in these patients remained unchanged
(0-1 (0-3)) from the initial value in the group of 12
patients evaluated at the time of diagnosis (0-4
(2-2)). Interestingly, among the four patients with
the greatest progression of bone maturation, only
one (case 5) had a low final height at 2-2 standard
deviations below the normal mean.

The results for the patients in group 1 were also
compared with the initial data for patients in group 2
at the time of diagnosis when precocious puberty
had already accelerated bone maturation by more
than two years. The mean (SD) predicted final
height of patients in group 2 was -1-3 (0-2) below
the normal mean, a value significantly lower than
that calculated for patients in group 1 (0-1 (0-3))
after a much longer period of spontaneous progres-
sion of the disease (p<0-01). This comparison
indicates that, despite nearly three years exposure
to low or variable oestrogen activity in group 1,
growth had remained sufficient in relation to bone
maturation to permit a satisfactory mean final
height prediction. This had not been the case in
patients in group 2 seen after an average period of
only one year who presented with pronounced
oestrogen activity and rapidly progressing bone
maturation.

Discussion

The results of this study showed that mild forms of
central precocious puberty in girls can be identified
at the first examination. They seem to be charac-
terised by a combination of low plasma oestradiol
and somatomedin C, and normal or slightly ad-
vanced bone age at the time of diagnosis. We have
shown that the course of the disease in these cases is
different from the usually severe forms of
precocious puberty.

Bone maturation and height gain do not progress
in parallel when sex hormones are secreted before
puberty, and it is known that precocious puberty
may accelerate epiphyseal fusion and lead to a
reduction in final height. The fact that some patients
in this group initially presented with normal or close
to normal bone age provided an opportunity to
assess the effect of moderate oestrogen activity on
growth and to discuss the need for treatment with
luteinising hormone releasing hormone analogue.
The group of girls with mild precocious puberty seen
nine months after the onset of clinical evidence of
ovarian activity had only a moderate advance in
bone age. The predicted final height remained
normal. This indicates that height gain had been
appropriate for bone age progression during this
early period of the disease. This effect on skeletal
growth was probably caused by low circulating
oestradiol concentrations during the preceding year.
It is comparable with the changes observed during
the early period of normal puberty when growth
acceleration accompanies or even precedes the
appearance of sexual characteristics. Plasma
somatomedin C values increase during normal
puberty, and it has been suggested that this pheno-
menon in girls is mediated by the oestrogens
indirectly through increased secretion of growth
hormone rather than through a direct effect of
oestradiol. In the present report, the plasma somatomedin C
values were in the prepubertal range or slightly
raised in girls with mild forms of precocious puberty,
and pubertal in those with the severe form. A more
complete evaluation of growth hormone secretion
using spontaneous growth hormone profiles could
not be performed in these patients, but in view of
their plasma somatomedin C values it is possible
that the growth hormone secretion in the mild form
of precocious puberty did not increase to the extent
seen in normal puberty during the Tanner P3
stage or in patients with severe precocious
puberty. One might consider, therefore,
that in addition to bone age the circulating value of
plasma somatomedin C at the first examination
reflected the ovarian activity, hence the severity of
the disease. It is tempting to relate these data to
recently reported results of skeletal response to low
doses of oestrogens in girls with Turner's
syndrome. These authors reported a significant
acceleration of growth without a concomitant
change in plasma somatomedin C. When low doses
of ethinyleoestradiol were used in these patients,
growth rates increased without changes in bone
maturation or plasma somatomedin C concentra-
tion. In the present study, a similar course of events
occurred in the group of girls with less severe
precocious puberty. In contrast, when pronounced
oestrogen activity was present at first examination,
its effect was predominant on bone maturation,
leading to a reduced final height prediction. This
was because the growth rate was not appropriate for
bone age progression, in contrast to the group with
moderate precocious puberty.
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The spontaneous course of idiopathic precocious puberty in girls varies in presentation of symptoms and rate of progression: some cases show accelerated development while others may progress slowly or have totally regressive and slow rate of progression: some cases of mild precocious puberty at time of diagnosis did not develop into severe and rapidly progressing precocious puberty. Furthermore, the age distribution did not differ between the groups. We suggest that girls with such moderate forms of precocious puberty be followed up for at least one year before deciding whether or not to have treatment with luteinising hormone releasing hormone analogue. Such treatment may be delayed as long as the final height prediction can be closely followed. Regression of pubertal signs may occur. If treatment is decided upon, it may be appropriate to re-evaluate the hypophysseal ovarian activity after two years of follow up to avoid unduly prolonged treatment. Probably all of these factors should be taken into consideration before committing a girl with central precocious puberty to treatment with the analogue.

In conclusion, an untreated group of girls with idiopathic central precocious puberty and moderate ovarian activity was followed for a period of two years. The data obtained at their first examination and in the course of their disease showed that bone maturation and plasma somatomedin C values are helpful in identifying the less severe and potentially slowly progressing forms of central precocious puberty. These cases might not require immediate treatment with the luteinising hormone releasing hormone analogue and a close follow up may be preferred before treatment to evaluate their natural course.

We thank Mrs M Lacroix and C Chamot for secretarial assistance.

References


Correspondence and requests for reprints to Dr R Brauner, Unité d'Endocrinologie Pédiatrique et Diabete, Hôpital des Enfants Malades, 149 Rue de Sèvres, 75015, Paris, France.

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M Fontoura, R Brauner, C Prevot and R Rappaport

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