Transient pseudo-precocious puberty by probable oestrogen intake in 3 girls

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SUMMARY We report the clinical and laboratory findings in 3 prepubertal girls with transient signs of sexual precocity. Accidental oestrogen intake from contaminated food was the most likely cause, the luteinising hormone—releasing hormone test is useful in the diagnosis of such patients.

Case reports

Case 1. This 7-year-old girl had enlarged breasts with hyperpigmentation of the areola and genitalia. A month later she had vaginal bleeding lasting 3 days. Oestrogen ingestion by tablet or its absorption by ointments, creams, or powders was excluded. Her height (114 cm) and weight (18 kg) were on the 3rd centile. Physical examination showed slight breast enlargement (Tanner’s 2nd stage) with intense pigmentation of the mammillary areola and anogenital region; there was no pubic hair. Bone age was slightly retarded (5-9 years according to Greulich and Pyle). X-ray films of the skull and fundus of the uterine lower segment were normal. Rectal examination showed no pubic mass or uterine enlargement. Vaginal smear showed clear evidence of oestrogenisation. Levels of E_2 were normal for age (<10 pg/ml). Serum gonadotrophin levels after LH-RH injection (50 µg intravenously) were very low (Table).

Breast enlargement and areolar pigmentation had disappeared 5 months later and vaginal bleeding did not recur. Vaginal smear now showed absence of

Table  Serum gonadotrophin levels after LH-RH injection (50 µg intravenously)

<table>
<thead>
<tr>
<th>Case</th>
<th>At peak oestrogenisation</th>
<th>After complete oestrogenisation regression</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>FSH (mIU/ml)</td>
<td>LH (mIU/ml)</td>
</tr>
<tr>
<td></td>
<td>Basal</td>
<td>Maximum</td>
</tr>
<tr>
<td>1</td>
<td>1.8</td>
<td>2.9</td>
</tr>
<tr>
<td>2</td>
<td>&lt;1.5</td>
<td>&lt;1.5</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>
oestrogenisation. Serum gonadotrophin levels after LH-RH returned to normal values for age (Table). At follow-up, 2 years later, the girl showed no sign of sexual precocity.

Case 2. At age 9 months, this girl had vaginal bleeding lasting 2 days. Three weeks later she again had vaginal bleeding. There was slight breast enlargement (Tanner's 2nd stage) and hyperpigmentation of the areola and anogenital region; there was no pubic hair. Height (86 cm) and weight (11 kg) were on the 50th centile. Reportedly, there was no history of oestrogen intake. Bone age was appropriate for chronological age. X-ray films of the skull and fundus oculi were normal. Rectal examination and vaginal endoscopy were normal. Vaginal smear showed evidence of oestrogenisation. Levels of E2 were normal for age. Serum gonadotrophin levels after LH-RH injection (50 μg intravenously) were very low (Table).

Three months later, breast enlargement had disappeared, and pigmentation of the areola and genitalia was diminished; vaginal bleeding did not recur. Vaginal smear now showed absence of oestrogenisation. Serum gonadotrophin levels after LH-RH returned to normal (Table). Two years later, all signs of sexual precocity had disappeared.

Case 3. This 17-month-old girl had vaginal bleeding lasting 3 days, and recurring 20 days later. She showed slight breast enlargement (Tanner's 2nd stage), with marked pigmentation of the mammillary areola; there was no pubic hair. Height (78 cm) was on the 25th centile; weight (9·6 kg) was on the 10th centile. Reportedly, there was no history of oestrogen intake. Bone age was appropriate for chronological age. X-ray films of the skull, fundus oculi, brain computerised tomography scans, rectal examination, and vaginal endoscopy were normal. Vaginal smear showed pronounced oestrogenisation. Levels of E2 were normal for age. Serum gonadotrophin levels after LH-RH injection (50 μg intravenously) were very low (Table).

Four months later, the breast enlargement and areolar pigmentation had regressed; vaginal bleeding did not recur. It was not possible to give an LH-RH test or take a control vaginal smear.

Discussion
In these patients, the presence of breast enlargement, vaginal bleeding, and marked oestrogenisation on the vaginal epithelium might have suggested a possible initial stage of true precocious puberty, but this could be excluded because in none was there a sudden increase in stature or bone maturation, and in none was there gonadotrophin increase.

Premature thelarche could be excluded because such patients have normal pigmentation of the mammillary areola, no vaginal bleeding, absent or weak oestrogenisation on the vaginal smear, and normal values of LH and follicle-stimulating hormone (FSH) (or only an increase in FSH).

Clinical signs and some of the laboratory findings showed there was the possibility of an autonomous oestrogen-secreting benign ovarian follicular cyst, an oestrogen-producing ovarian tumour, or a feminising adrenal tumour: however, normal recto-abdominal bimanual examination, the presence of normal E2 levels, and the fact that the clinical and laboratory findings returned to normal within a few months excluded any of these.

In premature menarche, vaginal bleedings are cyclic, breast enlargement is absent, and gonadotrophin secretion is normal.

Our patients had strikingly similar features—namely, transient clinical and laboratory evidence of sexual precocity with spontaneous return to normal within a few months, intense pigmentation of the mammillary areola, and only episodic vaginal bleeding. All such features have been found in cases of documented oestrogen intake.1–4

Since in our patients information from the parents excluded oestrogen intake through dermatological preparations or contaminated drugs, the most likely explanation was that of ingestion of contaminated food; this seems particularly common in Italy, probably because of the widespread consumption of meat from very young animals which have been fed with oestrogens in order to accelerate growth.5 7

This interpretation was also strongly supported by the very peculiar response of gonadotrophins to LH-RH (Table): in each child, at the time that clinical and laboratory evidence showed oestrogenisation, serum gonadotrophin levels were very low and remained so after LH-RH injection; in Cases 1 and 2 gonadotrophin levels returned to normal values for age after signs of oestrogenisation had disappeared.

In prepubertal girls, the only two conditions in which gonadotrophin suppression is found in association with signs of isosexual precocity are that of oestrogen intake and oestrogen-producing tumours or cysts. Only the former possibility needed to be considered as in our patients the clinical and laboratory findings spontaneously returned to normal.

It seems likely that transient signs of pseudo-precocious puberty together with clinical and laboratory findings as present in our patients are caused by oestrogen intake, even if this is not fully documented. The transient suppression of gonadotrophin secretion, as shown in the LH-RH test, together with
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vaginal smear, at the beginning and at the end of the clinical course, appears to be particularly helpful in the diagnosis.

References


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Successful treatment of gallstones with bile acids in obese adolescents

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Summary Six obese adolescents (4 girls, 2 boys) with radiolucent gallstones were treated with bile acids (chenodeoxycholic or ursodeoxycholic acid). Each had lithogenic bile and no predisposing factors for pigment stone formation. Within 12 months, the bile became unsaturated with cholesterol and the gallstones had disappeared in 4 cases and were decreased in size in two.

Cholesterol gallstones are rare in childhood even in such populations as the Pima Indians who have a high prevalence of the disease. Nevertheless, obesity predisposes to early appearance.

In obese adults cholesterol gallstones exhibit a poor response to treatment with bile acids, since secretion of lithogenic bile persists even if high doses of chenodeoxycholic acid (CDCA) are administered.

Six adolescents under age 14 years have been referred to our outpatient clinic for treatment of symptomatic radiolucent gallstones during the last 3 years. Each was obese and had bile supersaturated with cholesterol.

Treatment with bile acids, CDCA, or ursodeoxycholic acid (UDCA) was successful, and the bile, initially lithogenic, became unsaturated with cholesterol, and gallstones disappeared or decreased in size between 6 and 12 months later.

Patients, methods, results

The clinical data for the patients are shown in Table 1. In each case, gallstones were suspected on the basis of at least one episode of biliary colic and were diagnosed by cholecystography. Stone radioluency was confirmed by plain x-ray films of the abdomen. Liver function tests, plasma cholesterol levels, and triglycerides were normal. Erythrocyte defects leading to increased haemolysis could be excluded by indices of erythrocytes, reticulocyte

Table 1 Clinical data and effect of treatment

<table>
<thead>
<tr>
<th>Case</th>
<th>Age (years)</th>
<th>Sex</th>
<th>Ideal weight (%)</th>
<th>Drug</th>
<th>Stones Number</th>
<th>Response (dissolution)</th>
<th>Saturation index</th>
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</thead>
<tbody>
<tr>
<td>1</td>
<td>12</td>
<td>F</td>
<td>144</td>
<td>CDCA</td>
<td>Single 10</td>
<td>Partial</td>
<td>1.55</td>
</tr>
<tr>
<td>2</td>
<td>12</td>
<td>M</td>
<td>139</td>
<td>CDCA</td>
<td>Multiple 8</td>
<td>Complete</td>
<td>1.28</td>
</tr>
<tr>
<td>3</td>
<td>12</td>
<td>F</td>
<td>153</td>
<td>CDCA</td>
<td>Multiple 5</td>
<td>Complete</td>
<td>1.31</td>
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<tr>
<td>4</td>
<td>14</td>
<td>F</td>
<td>145</td>
<td>UDCA</td>
<td>Single 12</td>
<td>Partial</td>
<td>1.47</td>
</tr>
<tr>
<td>5</td>
<td>11</td>
<td>F</td>
<td>136</td>
<td>UDCA</td>
<td>Multiple 5</td>
<td>Complete</td>
<td>1.20</td>
</tr>
<tr>
<td>6</td>
<td>14</td>
<td>M</td>
<td>130</td>
<td>UDCA</td>
<td>Single 9</td>
<td>Partial</td>
<td>1.25</td>
</tr>
</tbody>
</table>

CDCA = chenodeoxycholic acid, UDCA = ursodeoxycholic acid.

*Size, diameter of largest stone.
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