DISCORDANT PATTERNS OF HYPERPROLACTINAEMIA AND GALACTORRHOEA IN SECONDARY AMENORRHOEA

By

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ABSTRACT

Hyperprolactinaemia occurred in 40 of 123 unselected patients (33%) with functional secondary amenorrhoea. Galactorrhoea was present only in 15 of these patients (38%). On the other hand, galactorrhoea was found in 10 of 83 euprolactinaemic patients (12%). The frequency and severity of hyperprolactinaemia and galactorrhoea dissociated in various forms of amenorrhoea. Anorexia nervosa was characterized by euprolactinaemia and the absence of galactorrhoea. Self-induced weight loss resulted in amenorrhoea with a moderate degree of hyperprolactinaemia in 23% of the cases. Yet, galactorrhoea was uncommon (1.6%). Amenorrhoea following stress was also associated with moderate hyperprolactinaemia in 31% of patients and a low frequency of galactorrhoea. By contrast, both hyperprolactinaemia and galactorrhoea occurred more frequently (36%) and were more severe in patients who had post-pill amenorrhoea, but still 50% of hyperprolactinaemic patients had no galactorrhoea and 28% of euprolactinaemic patients had galactorrhoea. This discordance was accentuated in those patients who had been pregnant even if pregnancy did not immediately precede amenorrhoea. Galactorrhoea (63%) and hyperprolactinaemia (36%) were common in these patients and very high serum prolactin values were sometimes seen. Our results point to different mechanisms involved in the regulation of hypothalamic pituitary function and breast secretion in various forms of secondary amenorrhoea, and they may help select patients in whom the prolactin assay is likely to identify indication for specific treatment.
Hyperprolactinaemia has generally been ascribed to pregnancy, normal and inappropriate lactation (Hwang et al. 1971; Besser et al. 1972; Thorner et al. 1974; Del Pozo et al. 1974). Several groups have recently shown that amenorrhoea without galactorrhoea may be associated with hyperprolactinaemia (Seppälä et al. 1975; Franks et al. 1975; Bohnet et al. 1975), but the occurrence of hyperprolactinaemia and its relation to galactorrhoea have not been established in various forms of amenorrhoea. We report results demonstrating that, in secondary amenorrhoea, hyperprolactinaemia and galactorrhoea show discordant profiles depending on certain anamnestic factors.

PATIENTS AND METHODS

At the end of 1976 there were 123 patients with functional secondary amenorrhoea recorded at the Hormone Outpatient Unit of the I and II Departments of Obstetrics and Gynaecology, University Central Hospital, Helsinki. In all cases amenorrhoea had persisted for at least 6 months. The major clinical features are listed in Table 1. In particular, we paid attention to the occurrence of anorexia nervosa, self-induced weight loss by at least 10% of body weight, previous use of oral contraceptives and pregnancies before the onset of amenorrhoea.

Table 1.
Clinical details of 123 women with secondary amenorrhoea.

<table>
<thead>
<tr>
<th>Anamnestic and clinical features</th>
<th>Total No. of patients</th>
<th>Hyperprolactinaemia (No. (%))</th>
<th>Mean (± sem) of the highest individual prolactin levels (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia nervosa</td>
<td>5</td>
<td>0 (0)</td>
<td>22.2 ± 3.9</td>
</tr>
<tr>
<td>Self-induced weight loss</td>
<td>61</td>
<td>14 (23)</td>
<td>21.7 ± 1.7</td>
</tr>
<tr>
<td>Stress</td>
<td>13</td>
<td>4 (31)</td>
<td>27.6 ± 4.5</td>
</tr>
<tr>
<td>Oral contraceptives</td>
<td>28</td>
<td>10 (36)</td>
<td>87.5 ± 42.6</td>
</tr>
<tr>
<td>Previously pregnant</td>
<td>19</td>
<td>7 (37)</td>
<td>122.0 ± 62.3</td>
</tr>
<tr>
<td>Chiari-Frommel syndrome</td>
<td>4</td>
<td>4 (100)</td>
<td>435.0 ± 255</td>
</tr>
<tr>
<td>Galactorrhoea</td>
<td>25</td>
<td>15 (60)</td>
<td>238.0 ± 80.8</td>
</tr>
<tr>
<td>spontaneous</td>
<td>15</td>
<td>14 (93)</td>
<td>330.1 ± 118</td>
</tr>
<tr>
<td>by squeezing only</td>
<td>10</td>
<td>1 (10)</td>
<td>84.3 ± 67.0</td>
</tr>
<tr>
<td>Pituitary tumour</td>
<td>5</td>
<td>5 (100)</td>
<td>825.0 ± 88.3</td>
</tr>
<tr>
<td>Idiopathic amenorrhoea</td>
<td>16</td>
<td>6 (38)</td>
<td>41.3 ± 11.5</td>
</tr>
<tr>
<td>Hirsute patients</td>
<td>9</td>
<td>5 (56)</td>
<td>121.9 ± 66.5</td>
</tr>
</tbody>
</table>
Five patients had anorexia nervosa. All had undergone psychiatric evaluation and presented typical loss of insight in distinction from 61 patients with self-induced weight loss. The commonest forms of stress preceding secondary amenorrhoea in 13 patients were related to environmental change and exhaustive studies. Twenty-eight patients had used oral contraceptives and 19 had one or several previous pregnancies. Nine patients were hirsute and one of them had polycystic ovaries at operation. In 16 patients no specific cause or clinical feature could be demonstrated and they were classified as having idiopathic secondary amenorrhoea. There were 36 patients in whom only one factor was identified, while the other patients showed at least two features. Accordingly, the patients were classified into one or several groups depending on the number of anamnestic and clinical factors present in each case.

All patients were examined for the occurrence of galactorrhoea, both spontaneous and while squeezing. Serum prolactin levels were measured by homologous radio-immunoassay (prolactin standard V.I.S. 3, NIAMDD, Bethesda, Md.) as described previously (Seppälä et al. 1975). Usually 3 to 6 samples were taken in each case and the highest observed levels were used to analyze between-group differences. The upper normal serum prolactin level was 30 ng/ml, and higher values were considered to indicate hyperprolactinaemia. The coefficient of intra-assay variation was 8–12%, and for inter-assay variation it was 18%.

RESULTS

Total series

Hyperprolactinaemia was occasionally found in 40 of 123 patients (33%). There was great variation in individual prolactin levels. Patients with levels over 120 ng/ml had hyperprolactinaemia in most specimens, whereas those with peak levels at 60 ng/ml usually also had normal levels in some samples. Among the 40 hyperprolactinaemic patients there were 15 who had demonstrable galactorrhoea (38%), and 25 had not. Galactorrhoea was found in 10 patients whose prolactin values were normal in all samples. Thus, 10 out of 25 patients (40%) with galactorrhoea had normal serum prolactin levels.

Anorexia nervosa

Patients with anorexia nervosa had normal prolactin levels and none had galactorrhoea. The mean of the highest recorded prolactin concentrations was 22 ng/ml (see Table 1).

Self-induced weight loss

Hyperprolactinaemia was found in 14 of 61 patients (23%). It was always moderate and there was no value exceeding 100 ng/ml. The mean of the highest individual prolactin levels was 22 ng/ml. Galactorrhoea was rare (1.6%) in spite of the fact that 8 patients had used oral contraceptives and 5 had been pregnant. No patient had spontaneous galactorrhoea and 1 patient had squeezing galactorrhoea with normal serum prolactin concentration (Fig. 1).
Fig. 1.
The occurrence of hyperprolactinaemia and galactorrhoea in 123 patients with secondary amenorrhoea.

**Stress**

Hyperprolactinaemia was found in 4 of 18 patients (31%) with stress related amenorrhoea. One euprolactinaemic patient with no other anamnestic factor had squeezing galactorrhoea. Hyperprolactinaemia was moderate when it occurred and the prolactin level never exceeded 100 ng/ml. The mean of the highest individual prolactin concentrations was 28 ng/ml (Table 1).

**Post-pill amenorrhoea**

Amenorrhoea following the use of oral contraceptives was related to hyperprolactinaemia in 10 of 28 patients (36%). Of these 5 had galactorrhoea and 5 had not. Spontaneous galactorrhoea occurred in 2 patients with a normal serum prolactin level. One of them had never been pregnant. Squeezing galactorrhoea was demonstrated in 3 other euprolactinaemic patients. The mean of the highest individual prolactin concentrations was 88 ng/ml, and 6 out of 10 hyperprolactinaemic patients had levels higher than 100 ng/ml.

**The effect of previous pregnancy**

Nineteen patients had been pregnant. Seven had hyperprolactinaemia (37%). Spontaneous galactorrhoea was found in 6 hyperprolactinaemic and 2 euprolactinaemic patients and 4 other euprolactinaemic patients had squeezing galactorrhoea. Thus, half of euprolactinaemic patients had demonstrable galactorrhoea (Fig. 1). Six of 7 hyperprolactinaemic patients had levels over 100 ng/ml, the highest level being 1200 ng/ml. The mean of the highest individual prolactin concentrations was 88 ng/ml.
lactin concentrations was 122 ng/ml (Table 1). There were 4 patients with the Chiari-Frommel syndrome. Their mean serum prolactin level was as high as 435 ng/ml.

Pituitary tumours

Five patients (4%\%) had a pituitary tumour. Galactorrhoea was present in three cases. In two of them amenorrhoea had persisted without galactorrhoea for 6 and 12 months, and there was no evidence for a pituitary tumour at that time. Galactorrhoea appeared after oestrogen replacement therapy and, 1 and 2 years later, pituitary expansion was eventually demonstrated by tomography of the sella. All these patients had high serum prolactin levels ranging from 145 to 620 ng/ml (Table 1).

Idiopathic amenorrhoea

No galactorrhoea occurred in this group of 16 patients. Hyperprolactinaemia was found in 6 patients (38\%). The mean serum prolactin level was 41 ng/ml.

Hirsute patients

Five of 9 hirsute patients (56\%) were hyperprolactinaemic and 2 of them had galactorrhoea. The mean prolactin concentration was 122 ng/ml (Table 1). The patient with polycystic ovaries had normal FSH and LH levels. Her plasma testosterone as well as urinary 17-ketosteroid excretion were also within the normal range at the time her serum prolactin concentration was elevated (48 ng/ml).

DISCUSSION

Hyperprolactinaemia was demonstrated in 33\% of unselected patients with secondary amenorrhoea. Yet, galactorrhoea was found only in 38\% of hyperprolactinaemic patients. This figure is very similar to that reported by Jacobs et al. (1976). The low frequency of galactorrhoea in hyperprolactinaemic patients was especially striking in amenorrhoea related to self-induced weight loss and stress. Stress itself can cause hyperprolactinaemia (Noel et al. 1972) which does not seem to readily induce galactorrhoea. We have seen some patients in whom galactorrhoea appeared after oestrogen replacement therapy had been discontinued. Oestrogens exert a tonic stimulus to the pituitary galactotrophs (Robyn et al. 1973), and this probably explains why amenorrhoea following the use of oral contraceptives was frequently related to galactorrhoea and hyperprolactinaemia. But, there were still 50\% of hyperprolactinaemic patients with post-pill amenorrhoea and no galactorrhoea.

Another remarkable group of patients had galactorrhoea in the presence of normal serum prolactin levels. Most of these patients had been pregnant. It
has been shown that prolactin levels usually return to normal during prolonged breast feeding and, when 12 weeks have elapsed from delivery the levels do not even rise in response to suckling (Friesen et al. 1973). The presence of galactorrhoea in euprolactinaemic patients is likely to reflect a situation in which pregnancy associated factors have primed the mammary gland to secrete in the presence of normal serum prolactin level. But, this does not explain euprolactinaemic galactorrhoea in 4 patients who had never been pregnant.

A third group of interest was hirsute women. In a preliminary communication (Seppälä & Hirvonen 1975) we reported raised prolactin levels in 5 of 6 hirsute women. Elevated levels in 5 of 9 additional patients in this series extend this finding. The classic report of Forbes et al. (1954) described an association between hirsutism, polycystic ovaries, galactorrhoea and amenorrhoea in patients with or without a pituitary tumour. We found raised prolactin levels in hirsute amenorrhoea patients with or without galactorrhoea. Prolactin seems to have a synergistic action with LH on testosterone secretion in the male (Rubin et al. 1975), but no similar action has been demonstrated in the female (Seppälä et al. 1976). This is not surprising, since 60% of the blood production rate of testosterone in the female is derived from the androstenedione pool in peripheral tissues (Horton & Tait 1966), which makes the regulation of testosterone synthesis and metabolism more complex in the female.

Our results show that galactorrhoea alone does not serve as a reliable marker of hyperprolactinaemia, and they point to different mechanisms in the regulation of hypothalamic-pituitary function and breast secretion in various forms of secondary amenorrhoea. The prolactin assay has become an important adjunct in the management of patients with amenorrhoea so as to select patients for specific treatment.

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