Hyponatraemia, diabetes mellitus, hyperprolactinaemia, retarded growth and delayed puberty in a 14 year old girl.

Effect of bromocriptine treatment

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Abstract. Investigations in a 14 year old girl with arrested growth for 2 years, delayed pubertal development, hyponatraemia without thirst, diabetes mellitus and hyperlipaemia are reported. The hyponatraemia was accompanied by a low vasopressin concentration with an abnormal response to thirst, high plasma renin but normal plasma aldosterone concentrations. Treatment with vasopressin and increased fluid intake decreased serum sodium levels. Serum gonadotrophins were low; GH response during an insulin tolerance test was subnormal and basal serum Prl concentration was elevated. Bone age, thyroid function and adrenal function were normal. After initiation of bromocriptine treatment her growth accelerated and regular menstruations commenced. The serum gonadotrophin levels increased and showed pulsatile release. A hypothalamic disorder is suggested, but no cerebral lesion could be demonstrated.

Hypothalamic diseases are often associated with hyponatraemia, high serum osmolarity, high plasma renin concentration, and normal plasma aldosterone concentration (Alford et al. 1973; Avioli et al. 1962; DeRubertis et al. 1971, 1974; Halter et al. 1977; Kastin et al. 1965; Mahoney & Goodman 1968; Sridhar et al. 1974; Travis et al. 1967) but normal blood pressure. Disorders involving the central nervous system have also been associated with diabetes mellitus (DeRubertis et al. 1974; Halter et al. 1977) and with hyperprolactinaemia and delayed puberty (Thorner et al. 1974).

We report investigations on a 14 year old girl with a polyendocrine disorder. She has hyponatraemia without thirst, diabetes mellitus, hyperlipaemia, hyperprolactinaemia, retarded growth and delayed puberty. This multiplicity of symptoms in a single patient has not been reported previously. Furthermore, she has been followed for 3 years and growth and pubertal development accelerated during bromocriptine treatment.

Case Report

The patient, a 14 year old girl, was referred because of diabetes mellitus. Family and medical history until the age of 6 years was uneventful. At the age of 6 years she had an unknown severe infectious disease with cerebral involvement. She was not hospitalized and no further investigations were made. From the age of 6 years she developed moderate obesity. At the age of 11 years puberty commenced with growth of pubic and axillary hair and mammary enlargement. After a normal growth up to the age of 12 years growth and pubertal development ceased. Menarche was absent.

The main complaints were her tiredness, thirst and weight loss over a few months. On admission her weight was 36 kg and her height was 142.5 cm (Fig. 1). She was short-necked with adipose trunk and slim extremities. Her movements were slow and her facial expression was listless. Her mental capacity was normal. She had some pubic hair and mammary enlargement (Tanner stage 2–3) without galactorrhoea. Her bone age was 14 years, blood pressure, serum creatinine and liver status were normal. Visual field examination, EEG, X-ray of the sella turcica, pneumoencephalography and computerized to-
The maximum GH response was determined by measuring plasma GH concentrations during an insulin tolerance test: the patient received 12 IU regular insulin iv and during the first 60 min blood glucose level decreased from 12.2 to 4.7 mmol/l. During the next 2.5 h three doses of regular insulin iv (12 IU + 8 IU + 12 IU) was needed to reach a blood glucose level of 1.7 mmol/l associated with sweating. Furthermore, plasma GH concentrations were measured during an iv infusion of t-arginine 0.5 g per kg body weight for 30 min.

Prl, TSH and gonadotrophin responses were measured before and after iv administration of 100 µg of TRH and 100 µg L.RH, respectively.

Spontaneous variations in gonadotrophin release were recorded by measuring gonadotrophin concentrations every 20 min for a 4 h period before, and 3 and 6 months after bromocriptine treatment.

Endogenous insulin secretion was estimated by measuring the serum concentration of immunoreactive C-peptide after iv injection of 1 mg glucagon (Faber & Binder 1977).

Results

Hypernatraemia

On a non-discriminate sodium and water intake the serum concentration of sodium was 165–175 mmol/l. The serum concentration of potassium was normal. The serum osmolality was 309 mOsm/kg, and simultaneously the osmolality of a 24 h urine sample (670 ml) was 743 mOsm/kg. The plasma renin concentration was high. In contrast the plasma aldosterone concentration was normal (Table 1). At the age of 15 years her endogenous vasopressin secretion was investigated after 4 days withdrawal of exogenous vasopressin. The basal vasopressin concentration was low. After 19 h of water abstinence urine osmolality had increased, with only a small increase in serum osmolality and an insignificant rise in vasopressin concentration (Table 2).

During vasopressin treatment (desamino-D-arginine-8-vasopressinacetate (Minurin®) 20–25 µg/h) and increased fluid intake (at least 2 l/24 h) the serum sodium level decreased to around 150 mmol/l and the serum osmolality decreased to 264–297 mOsm/kg. The osmolality of the urine showed major fluctuations (311–538 mOsm/kg).

During vasopressin treatment the plasma renin concentration was 150–590 mU/l and a significant correlation between plasma renin concentration and serum sodium concentration was demon-
### Table 1.
Serum concentrations of pituitary hormones, oestradiol, cortisol, aldosterone and renin at various ages and before and during bromocriptine treatment.

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>14</th>
<th>14½</th>
<th>15½</th>
<th>15¾</th>
<th>16</th>
<th>Normal range(^5)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment</td>
<td>Insulin vasopressin</td>
<td>Insulin vasopressin oestradiol</td>
<td>vasopressin</td>
<td>Vasopressin bromocriptine</td>
<td>Vasopressin bromocriptine</td>
<td></td>
</tr>
<tr>
<td>LH basal IU/l</td>
<td>2.4</td>
<td>&lt; 2.0</td>
<td>2.1–2.8</td>
<td>6.8–13.0</td>
<td>1.9–11.9</td>
<td>1.9–11.9</td>
</tr>
<tr>
<td>LRH max.(^1) IU/l</td>
<td>22.0</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 8.2</td>
<td>&gt; 8.2</td>
</tr>
<tr>
<td>FSH basal IU/l</td>
<td>5.3</td>
<td>&lt; 2.0</td>
<td>1.3–1.8</td>
<td>5.5–6.9</td>
<td>6.4–8.6</td>
<td>1.4–7.4</td>
</tr>
<tr>
<td>LRH max.(^1) IU/l</td>
<td>12.6</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 3.9</td>
<td>&gt; 3.9</td>
</tr>
<tr>
<td>GH basal µg/l</td>
<td>2.4</td>
<td>4.7</td>
<td>2.3</td>
<td>2.5</td>
<td>1.0</td>
<td>&lt; 6</td>
</tr>
<tr>
<td>insulin max.(^2) µg/l</td>
<td>7.1</td>
<td>9.8</td>
<td></td>
<td></td>
<td></td>
<td>&gt; 10</td>
</tr>
<tr>
<td>arginine max.(^3) µg/l</td>
<td>11.5</td>
<td>4.0</td>
<td>7.2</td>
<td>4.2</td>
<td>10</td>
<td>&gt; 10</td>
</tr>
<tr>
<td>Prl basal µg/l</td>
<td>294</td>
<td>220</td>
<td>4</td>
<td></td>
<td></td>
<td>7–30</td>
</tr>
<tr>
<td>TRH max.(^4) µg/l</td>
<td>240</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TSH basal mU/l</td>
<td>1.8</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 1.9</td>
<td></td>
</tr>
<tr>
<td>TRH max.(^4) mU/l</td>
<td>19.4</td>
<td></td>
<td></td>
<td></td>
<td>6–18</td>
<td></td>
</tr>
<tr>
<td>Oestradiol-17β nmol/l</td>
<td></td>
<td>&lt;0.035</td>
<td>0.128</td>
<td>0.121</td>
<td>0.08–0.40</td>
<td></td>
</tr>
<tr>
<td>Cortisol basal nmol/l</td>
<td></td>
<td>601</td>
<td></td>
<td></td>
<td>240–850</td>
<td></td>
</tr>
<tr>
<td>insulin max.(^2) nmol/l</td>
<td></td>
<td>1457</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACTH basal ng/l</td>
<td>60</td>
<td></td>
<td></td>
<td></td>
<td>&lt; 76</td>
<td></td>
</tr>
<tr>
<td>insulin max.(^2) ng/l</td>
<td>291</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aldosterone pmol/l</td>
<td>222</td>
<td>195</td>
<td>334</td>
<td>220</td>
<td>83–500</td>
<td></td>
</tr>
<tr>
<td>Renin mIU/l</td>
<td>460</td>
<td>172</td>
<td>157</td>
<td>199</td>
<td>6–60</td>
<td></td>
</tr>
</tbody>
</table>

1 Peak level during iv LRH-test with 100 µg LRH.  
2 Peak level during insulin-induced hypoglycaemia.  
3 Peak level during iv infusion of l-arginine 0.5 g/kg.  
4 Peak level during iv TRH-test with 100 µg TRH.  
5 Normal pre-menopausal women, follicular phase of the cycle.

strated (r = 0.78, n = 14, P < 0.001). The plasma aldosterone concentration remained normal in spite of the high plasma renin levels. During vasopressin treatment and increased water intake her slow and listless movements disappeared and she became more alert. Even though the serum sodium concentration remained slightly above normal she did not complain of thirst.

Bromocriptine treatment had no influence on plasma concentrations of renin and aldosterone.

**Pituitary function**

The patient, in pubertal arrest, had lower plasma concentrations of LH, FSH and oestradiol-17β and very elevated plasma Prl levels (224–295 µg/l). The LH and FSH responded normally to stimulation with LRH. A blunted GH response to insulin-induced hypoglycaemia and to arginine infusion was seen, which is in accordance with the slow growth (Table 1). Serum somatomedin concentration was low, 0.56 U/ml (normal range 0.8–1.2). TSH, ACTH and cortisol were within normal range. TSH response to TRH and cortisol and ACTH response to insulin-induced hypoglycaemia were normal.

Bromocriptine, a dopamine agonist, suppresses prolactin secretion. Bromocriptine treatment was started at the age of 15½ years with 2.5 mg daily
Table 2. 
Vasopressin secretion after 4 days' withdrawal of exogenous vasopressin.

<table>
<thead>
<tr>
<th></th>
<th>Initial</th>
<th>After 19 h water abstinence</th>
<th>1 h after ingestion of 500 ml water</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arginine vasopressin (ng/l)</td>
<td>2.3</td>
<td>3.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Serum sodium (mmol/l)</td>
<td>165</td>
<td>165</td>
<td></td>
</tr>
<tr>
<td>Serum osmolality (mOsm/kg)</td>
<td>345</td>
<td>364</td>
<td>356</td>
</tr>
<tr>
<td>Urinary osmolality (mOsm/kg)</td>
<td>460</td>
<td>840</td>
<td>770</td>
</tr>
</tbody>
</table>

and increased to 7.5 mg daily. The drug was well tolerated with no side-effects. After 3 months of treatment the patient had her first period. At this time the LH, FSH and oestadiol-17β levels had increased and LH showed a pulsatile release (Fig. 2). A dramatic fall in plasma Prl levels was seen (Table 1). From the age of 14 to 15½ years she had grown 3.5 cm in height and gained 13 kg in weight (Fig. 1). After 9 months of bromocriptine treatment the GH response to arginine infusion was still subnormal (Table 1), even though she had grown 5 cm in height and had increased mammary enlargement and increased growth of pubic and axillary hair.

*Diabetes mellitus and hyperlipaemia*

On admission her blood glucose level was 17.2 mmol/l without ketoacidosis. During 6 weeks' diet and insulin treatment (zinc insulin + regular insulin; 24 IU per day in two doses) blood glucose levels remained high (8–14 mmol/l) but without major fluctuations during the day. The urinary excretion of glucose decreased from 100 mmol/24 h to below 20 mmol/24 h. The dose of insulin was then gradually increased to 38 IU per day and blood glucose levels decreased to 5–10 mmol/l and urine became free of glucose. After 2 weeks the insulin dose was reduced to 28 IU per day. Blood glucose concentrations were normal and there was no urinary glucose excretion.

After 2 months of insulin treatment the C-peptide response to glucagon was measured. Basal plasma C-peptide concentration was normal (0.80 nmol/l) and a normal response (1.92 nmol/l at 10 min) to glucagon was seen. Before insulin treatment her plasma insulin concentration was high (0.12 nmol/l).

Insulin treatment was withdrawn after 8 months and blood glucose levels remained within the normal range. However, at the age of 16½ years her glucose tolerance test was slightly diabetic.

Before insulin treatment the serum cholesterol concentration was 9.9 mmol/l; during treatment 7.1–10.5 mmol/l and after treatment 6.1–11.8 mmol/l. Before insulin treatment the serum triglyceride concentration was 5.1 mmol/l; during treatment 1.6–4.5 mmol/l and after treatment 1.4–10.9 mmol/l. Treatment with bromocriptine did not change cholesterol nor triglyceride levels.

**Discussion**

The remarkable findings in this patient were a) hypernatraemia accompanied by a subnormal vasopressin response and high plasma renin concentration without any change in plasma aldosterone concentration and blood pressure, b) pubertal arrest at an early stage of puberty accompanied by low oestrogens and gonadotrophins, hyperprolac-

![Graph](image_url)
tinaemia and a subnormal GH response, c) diabetes mellitus accompanied by normal insulin secretion and hyperlipaemia, d) improved feminisation and growth during bromocriptine treatment.

In the rat, a lesion of the periventricular area of the third ventricle induced hypernatraemia without thirst (Buggy & Johnson 1977). A similar syndrome has been reported in man and is a characteristic symptom in hypothalamic diseases (DeRubertis et al. 1971, 1974; Halter et al. 1977; Sridhar et al. 1974; Travis et al. 1967). However, it has also been found in patients without any known cerebral lesions (Alford et al. 1973). In patients with hypernatraemia, vasopressin secretion in relation to changes in serum and urine osmolality during an osmotic load has suggested that the elevated serum sodium may be due to a decreased sensitivity of the osmoreceptive cells (DeRubertis et al. 1971; Halter et al. 1977; Sridhar et al. 1974). Our patient had low basal vasopressin concentration and an insignificant increase in vasopressin levels during a water deprivation test despite a slight increase in serum osmolality. From these results it is not possible to discriminate between damage of the osmoreceptive cells and the vasopressin secreting neurons. The apparent contradiction between elevated plasma renin concentration and normal plasma aldosterone concentration is unexplained but in agreement with other reports (Alford et al. 1973; Mahoney & Goodman 1968; Travis et al. 1967).

These results might be explained by a hypothalamic factor influencing the normal relationship between renin, angiotensin and aldosterone.

Hyperprolactinaemia has been found in patients with pituitary and hypothalamic diseases (Thorner et al. 1974). As no hypophyseal tumour was found in our patient, her hyperprolactinaemia might be due to a decreased hypothalamic inhibition of Prl secretion. Hyperprolactinaemia is known to be accompanied by suppressed gonadal function (Thorner et al. 1974). Initially, our patient had low levels of oestrogens and delayed puberty. No improvement was noted during the first 1½ years of regulation of carbohydrate, lipid and electrolyte metabolism. However, after only 3 months of bromocriptine treatment, resulting in normalization of serum prolactin, gonadotrophin and oestrogen levels, regular menstruations commenced. Thus, we suggest that her hypogonadism may be secondary to her hyperprolactinaemia either by affecting the gonadotrophin secretion or influencing the hormone secretion of the ovaries. Her retarded growth was characterized by a subnormal response of GH to hypoglycaemia and arginine infusion, normal bone development and low somatomedin concentrations. The growth did not improve after regulation of her hyperglycaemia and hypernatraemia. However, a growth spurt occurred during the first 9 months of bromocriptine treatment. Therefore one might suggest that it was related to the increased oestrogen levels recorded during this period.

In patients with chronic hypernatraemia the blood glucose levels are usually normal (Alford et al. 1973; DeRubertis et al. 1971; Kastin et al. 1965; Mahoney & Goodman 1968; Sridhar et al. 1974; Travis et al. 1967), but hyperglycaemia has been reported (DeRubertis et al. 1974; Halter et al. 1977) and one patient died in a diabetic hyperosmolar coma. The decreased glucose tolerance in our patient may be caused by insulin deficiency and decreased insulin secretion. However, this is not very likely, because of the high plasma insulin concentration before treatment and the normal C-peptide response to glucagon after 2 months of diet and insulin treatment. Furthermore, after 3 years of observation the fasting blood glucose levels are still normal. The decreased glucose tolerance might rather be caused by a decreased cellular sensitivity to insulin. This is underlined by the fact that large amounts of insulin were necessary to induce hypoglycaemia. In animals there is some evidence for a hypothalamic regulation of the release of insulin and glucagon (Moltz et al. 1975) and in our patient the diabetes mellitus may perhaps be of cerebral origin. Like other investigators (DeRubertis et al. 1974; Halter et al. 1977; Sridhar et al. 1974) we found hypertriglyceridaemia in our patient. This may be caused by a decreased insulin action on the lipid metabolizing cells. The normalization of the serum Prl level did not improve glucose tolerance or lower triglyceride levels. Therefore, it is unlikely that prolactin influences the cellular sensitivity to insulin.

From the history, photos of the patient at different ages and the initial normal growth curve we suggest that her condition was acquired. Three years after her first symptom no intracranial lesion has been detected. Similar syndromes have been reported in patients where histological examinations of the brain have shown lesions caused by inflammation (Sridhar et al. 1974; Travis et al. 1967). This might be the cause in our patient.
Acknowledgments

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References


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