ACTH and prolactin deficiency

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Abstract. A 35 year old woman suffering from ACTH and prolactin (Prl) deficiency is described. Her symptoms of adrenal insufficiency appeared gradually after her first pregnancy in 1970; however, she conceived twice more and delivered healthy babies in 1972 and 1974, which she could not breast feed due to lack of milk. During an episode of pneumonia in 1977 she suffered acute adrenal insufficiency, after which she began treatment with hydrocortisone. Her pituitary reserve for TSH, GH, LH and FSH was normal, but her ACTH and Prl levels were undectable and did not respond to acute iv challenges of corticotrophin-releasing factor (CRF) and TRH, respectively. Autoantibodies, including antilactotroph titres, were negative, except for a positive pituitary immunofluorescence to ACTH. There was also no ACTH stimulation to a prolonged infusion of CRF followed by an acute iv bolus. These results, together with the gradual onset of symptoms which worsened after each pregnancy, suggest a possible autoimmune aetiology of her pituitary ACTH and Prl deficiencies.

Multiple pituitary hormone deficiencies constitute a relatively common finding in an endocrine clinic. Monotrophic deficiencies of each of the pituitary hormones have also been described over the last few years. Thus, isolated growth hormone (GH) and isolated gonadotrophin deficiencies are relatively common, while isolated thyrotrophin (TSH) deficiency is rare, and only a few cases of isolated prolactin (Prl) (Carlson et al. 1977; May et al. 1980; George et al. 1984) and adrenocorticotrophin (ACTH) deficiencies have been described (Steinberg et al. 1954; Richtsmeier et al. 1980; Stacpoole et al. 1982; Nakahara et al. 1983; Yoshida et al. 1983; Lytras et al. 1984). With the introduction of the new hypothalamic hormones as tools to investigate patients with so called ‘ACTH deficiency’, it is now becoming apparent that this is a heterogenous disorder of either pituitary or hypothalamic origin. In this latter case, the lacking peptide would be corticotrophin-releasing factor (CRF) and not ACTH.

We describe a patient who was found to exhibit a Prl deficiency and an adrenal cortical impairment, with normal GH, TSH, LH and FSH secretion, in whom CRF was administered, with the aim of trying to elucidate whether the abnormality was primarily pituitary or hypothalamic.

Case report

The patient is a 35 year old white female, who was admitted to the emergency room in 1977 with unconsciousness, hypotension, hypoglycaemia, hyponatraemia, hyperkalaemia, and pneumonia. She recovered completely with iv hydrocortisone, saline, glucose and penicillin. On direct questioning, she referred no head injury, but complained of lack of energy and 5 episodes of unconsciousness since 1970 after her first pregnancy. She had breast fed her first baby for a few days, but had to abandon it after developing mastitis. In 1972 she...
Table 1.
Hormonal responses to provocative tests of endocrine function.

<table>
<thead>
<tr>
<th>Tests</th>
<th>Time points (min)</th>
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<tbody>
<tr>
<td></td>
<td>-15</td>
</tr>
<tr>
<td>Free T₄, pmol/l (normal range)</td>
<td>18.1</td>
</tr>
<tr>
<td>Total T₃ nmol/l (normal range)</td>
<td>2.3</td>
</tr>
<tr>
<td>TRH (400 µg):</td>
<td></td>
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<tr>
<td>- TSH, mIU/l (normal range)</td>
<td></td>
</tr>
<tr>
<td>- PRL, µg/l (&lt;2.0 &lt;2.0 &lt;2.0 &lt;2.0 &lt;2.0 &lt;2.0 &lt;2.0</td>
<td></td>
</tr>
<tr>
<td>ITT (0.12 IU/kg body weight):</td>
<td></td>
</tr>
<tr>
<td>- glucose, mmol/l</td>
<td>4.4</td>
</tr>
<tr>
<td>- GH, mIU/l*</td>
<td></td>
</tr>
<tr>
<td>- cortisol, nmol/l (&lt;27.6 &lt;27.6 &lt;27.6 &lt;27.6 &lt;27.6 &lt;27.6 &lt;27.6</td>
<td>27.6</td>
</tr>
<tr>
<td>LRH (100 µg):</td>
<td></td>
</tr>
<tr>
<td>- LH, IU/l**</td>
<td>8.0</td>
</tr>
<tr>
<td>- FSH, IU/l***</td>
<td>3.6</td>
</tr>
</tbody>
</table>

* Normal response: peak > 14 mIU/l.
** Normal response in the early follicular phase: 3- to 4-fold from baseline.
*** Normal response in the early follicular phase: ½- to 2-fold from baseline.

delivered her second child, but this time she had no milk and developed amenorrhoea thereafter. Nevertheless, she conceived again and had a third healthy baby in 1974, whom she bottle fed due to lack of breast milk. All three deliveries were quite normal, with no excessive bleeding or other complications. From 1974 onwards, her tiredness and lack of energy increased, she was amenorrheic and referred a progressive loss of pubic and axillary hair. In 1977, she was found to exhibit a normal cortisol response to 4 consecutive injections of 1 mg of synthetic corticotrophin (Nuvachten®, Ciba-Geigy). She was diagnosed as suffering from ‘hypopituitarism’ and treated with hydrocortisone (30 mg/day), l-thyroxine (100 µg/day) and oral contraceptives. She improved dramatically on this treatment, her menses and body hair returned, blood pressure was normal and her tiredness and lack of energy disappeared. In January 1982, she stopped the oral contraceptives and menstruated spontaneously every 28-30 days. Seen in our clinic for the first time, the initial diagnosis was questioned and she was admitted to hospital for adequate endocrine assessment. l-thyroxine was also withdrawn. A skull X-ray and CT scan were reported normal. Results of endocrine investigations are seen in Table 1. Under dexamethasone cover, she responded adequately to 1 mg injections of synthetic corticotrophin (basal cortisol < 27.6 nmol/l; after 4 days treatment 715 nmol/l), thus demonstrating normal adrenal capacity for cortisol synthesis. Immunological investigations demonstrated negative results for thyroglobulin, microsomal, gastric parietal cell, pancreatic islet cell and Prl-cell antibodies, and positive pituitary immunofluorescence to ACTH. Two hundred µg iv of synthetic human CRF (Peninsula Lab., Belmont, CA, USA, dissolved in 0.8 ml of 0.02% HCl in 0.9% saline) elicted no response whatsoever of either cortisol or ACTH over 120 min. A second CRF test with 200 µg iv (Bachem, Torrance, CA, USA) after a 3 h infusion of CRF (45 µg dissolved in 28 ml of saline with 2 ml of human serum albumin at a rate of 15 µg/10 ml per h), again demonstrated no response of ACTH (<19 pg/ml), cortisol (<27.6 nmol/l) or PRL (<2 ng/l) throughout the 5 h period of study. This second infusion test was aimed at producing a more prolonged stimulation on supposedly chronically understimulated corticotrophs.

Assay methods

Commercial radioimmunoassay kits were used for measurements of free T₄ (twostep GammaCoat FT4 RIA kit, Clinical Assays, Travenol Lab., Inc., Cambridge, MA, USA), cortisol, TSH and total T₃ (Diagno-
tic Products Corp., Los Angeles, CA, USA), FSH, LH and Prl (Serono Diagnostics SA, France), and GH (Pharmacia Diagnostics AB, Uppsala, Sweden). ACTH was measured by an unextracted RIA, using Standard 74/555 supplied by the National Institute for Biological Studies and Controls (London), a commercially available antibody and tracer (CIS) and a Sepharose bound second antibody (Miles) to separate the free and bound fractions. Autoantibodies were kindly measured at the Department of Immunology of the Middlesex Hospital Medical School, London, UK (Profs. D. Doniach and G. F. Botazzo).

Discussion

An absence of ACTH and Prl responses to direct stimulation of the pituitary gland is described in a patient whose clinical course suggests a slowly progressive development of these deficiencies related to her pregnancies. Of interest is the very slow progressive nature of this patient’s disease over at least two and possibly even three pregnancies. Hypophysitis of pregnancy was suspected, and immunological studies were conducted with negative results except for positive pituitary ACTH immunofluorescence. However, it was not possible to know whether this positivity was due to a specific reaction or a non-specific positivity due to the attachment of the immunoglobulin through the Fc region (Pouplard et al. 1976). Thus, the suspected autoimmune aetiology which has been suggested in some cases of ACTH deficiency (Gossain & Rovner 1984; Kojima et al. 1982) is difficult to demonstrate.

The absent response of ACTH and cortisol to CRF would argue against a hypothalamic origin of our patient’s endocrine deficiency. This is further supported by the fact a 3 h infusion followed by an acute iv bolus did not elicit a rise in either of these hormones. If a long-standing CRF deficiency had been present in our patient a response to a prolonged CRF infusion would have been expected. Since a brief rise in Prl has been described after human CRF administration (Hermus et al. 1984), this lactotroph hormone was also measured throughout the prolonged CRF test, but remained undetectable.

Patients with isolated ACTH deficiency often exhibit a relatively increased resistance to stress and less blood sugar sensitivity to exogenous insulin administration, as compared to those with primary adrenal insufficiency. Our patient actually required a second dose of insulin to develop hypoglycaemia, and referred clinical symptoms compatible with adrenal insufficiency for at least 8 years prior to her adrenal ‘crisis’, which was precipitated by pneumonia. Only 3 cases of acute adrenal insufficiency were reported by Stacpoole et al. (1982) in their review of more than 40 cases, two following bacterial infections and one following a dental extraction.

Prl deficiency has been described in association with pseudohypoparathyroidism (Carlson et al. 1977) and in a series of non-endocrine disorders such as myotonic dystrophy (May et al. 1980) and stiff-man syndrome (George et al. 1984). The diagnosis of lactotroph deficiency is usually made on clinical grounds (inability to lactate) associated with a lack of Prl response to stimuli such as TRH. Apart from the patient described here, a further case of Prl and ACTH deficiency was recently described by Gossain & Rovner (1984); this young woman also suffered from primary autoimmune thyroiditis and hypothyroidism. The possibility of an autoimmune basis for her pituitary disorders was suggested, given her thyroid problem, and the development of clinically apparent symptoms of hormone deficiency following a pregnancy. It is known that autoimmune reactions are suppressed to some degree during pregnancy (Beer & Billingham 1971) and that autoimmune hypophysitis has been related to pregnancy (Richthmeier et al. 1980; Asa et al. 1981) as other autoimmune diseases. Despite the negative test for antilactotroph antibodies in the patient of Gossain & Rovner (1984) and our patient, the diagnosis of autoimmune hypophysitis cannot be excluded, since no strict correlation between the presence or absence of pituitary antibodies and altered pituitary function has been established (Botazzo & Doniach 1978). Possible explanations for this discordance, such as the greater importance of cell-mediated vs humoral factors in autoimmune pituitary disorders, and fall of antibody titres after destruction of target tissue, have been put forward (Carlson et al. 1977).

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References


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