Weight as the best standard for glomerular filtration in the newborn

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SUMMARY Adrenal function test results in a girl with Cushing's syndrome and a bronchial carcinoid tumour suggested pituitary dependent hypercortisolism. Resolution after excision of the tumour indicated that her condition had been caused by ectopic adrenocorticotropic hormone secretion. Conventional tests of adrenal function may be misleading in cases of adrenocorticotropic hormone secreting bronchial carcinoid tumours.

The aetiology of Cushing's syndrome can usually be determined from the serum adrenocorticotropic hormone concentration and the response of urinary corticosteroids to high dose dexamethasone and metyrapone. In some circumstances, however, these investigations may be misleading. We report a patient who seemed to have pituitary dependent hypercortisolism but was subsequently shown to have an adrenocorticotropic hormone secreting bronchial carcinoid tumour.
**Case report**

A 15 year old girl presented with a 14 month history of weight gain, hirsutism, acne, and striae and an 8 month history of secondary amenorrhea after menarche at the age of 14 years. Her height was 160 cm, weight 63-8 kg and pubertal stage P2G5. Examination showed central obesity, 'moon face', cervicothoracic fat pad, acne, hirsutism, and purple striae of breasts, thighs and abdomen. Her blood pressure was 130/85 mmHg.

A skull radiograph, tomography of the pituitary fossa, intravenous urogram, and computed tomography of the abdomen were normal. A chest radiograph showed a rounded lesion in the right lung. The urinary 5 hydroxyindoleacetic acid (5HIAA) concentration was raised at 15-9 mmol/mol creatinine (normal 0-4 mmol/mol creatinine).

Results of adrenal function tests are shown in the Table. Values of plasma cortisol and urinary cortisol derivatives (mainly cortisol itself and tetrahydrocortisol) were raised. Plasma adrenocorticotrophic hormone concentrations were moderately raised. Urinary cortisol derivative excretion was suppressed with high dose dexamethasone (8 mg daily) but not low dose dexamethasone (2 mg daily). Urinary cortisol precursors (mainly 11-deoxy cortisol, Compound S) and derivatives increased after she was given metyrapone (750 mg four hourly for 6 doses).

The tumour was excised and the postoperative period was uneventful. Six months later her weight had fallen to 48-6 kg and the stigmata of Cushing's syndrome, other than the striae, had disappeared. Plasma cortisol values and urinary corticosteroid excretion returned to normal.

**Pathological studies**

Conventional light microscopy showed the tumour to be a bronchial carcinoid. Histochemical investigations showed positive argyrophil and argentaffin staining of cytoplasmic granules. Round dense cytoplasmic neurosecretory granules were shown by electron microscopy. Immunohistochemical staining was positive for adrenocorticotrophic hormone and tumour tissue tested against a panel of monoclonal antibodies (Frenchay Hospital, Bristol) was positive to neuroectodermal markers UJ13A and H11.

Tumour extract contained immunoreactive 'N' terminal adrenocorticotrophic hormone, immunoreactive 'C' terminal adrenocorticotrophic hormone, immunoreactive β endorphin, and immunoreactive γ melanocyte stimulating hormone. Chromatography of adrenocorticotrophic hormone obtained from tumour tissue showed only a single band corresponding to 1–37 adrenocorticotrophic hormone. Plasma contained immunoreactive γ melanocyte stimulating hormone and immunoreactive β endorphin. (St Bartholomew's Hospital, London).

**Discussion**

Pituitary dependent hypercortisolism is usually associated with serum adrenocorticotrophic hormone concentrations of less than 200 ng/l, suppression of urinary cortisol derivatives with high dose dexamethasone, and increased urinary cortisol precursors and derivatives with metyrapone. Typical, in the ectopic adrenocorticotrophic hormone syndrome, serum adrenocorticotrophic hormone concentrations exceed 200 ng/l and urinary corti-

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**Table**  Adrenal function tests

<table>
<thead>
<tr>
<th>Day</th>
<th>Treatment</th>
<th>Urinary cortisol derivatives* (mmol/mmol creatinine)</th>
<th>Urinary cortisol precursors* (mmol/mmol creatinine)</th>
<th>Time</th>
<th>Serum adrenocorticotrophic hormone† (ng/l)</th>
<th>Plasma cortisol‡ (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Basal</td>
<td>13-4</td>
<td>0-5</td>
<td>1100</td>
<td>—</td>
<td>625</td>
</tr>
<tr>
<td>2</td>
<td>Basal</td>
<td>13-1</td>
<td>1-3</td>
<td>2400</td>
<td>170</td>
<td>478</td>
</tr>
<tr>
<td>3</td>
<td>Dexamethasone (0-5 mg 6 hourly)</td>
<td>—</td>
<td>—</td>
<td>0000</td>
<td>110</td>
<td>760</td>
</tr>
<tr>
<td>4</td>
<td>Dexamethasone (0-5 mg hourly)</td>
<td>14-7</td>
<td>0-5</td>
<td>2400</td>
<td>—</td>
<td>615</td>
</tr>
<tr>
<td>5</td>
<td>Dexamethasone (2 mg 6 hourly)</td>
<td>13-3</td>
<td>0-9</td>
<td>0000</td>
<td>160</td>
<td>302</td>
</tr>
<tr>
<td>6</td>
<td>Dexamethasone (2 mg hourly)</td>
<td>6-5</td>
<td>0-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Basal</td>
<td>15-7</td>
<td>0-4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Metyrapone (750 mg 4 hourly)</td>
<td>28-0</td>
<td>17-7</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Basal</td>
<td>77-0</td>
<td>4-3</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Normal, 1-0-3-8 mmol/mol creatinine.
†Normal, 0-2-0-6 mmol/mol creatinine.
‡Normal, <80 ng/l at 9:00 am.
§Normal, 130-660 mmol/l at 9:00 am.
costeroids are unaffected by high dose dexamethasone and metyrapone.

In our patient, the adrenal function tests were so consistent with pituitary disease that the pulmonary lesion was initially thought to be coincidental. However, the resolution of hypercortisolism after excision of a tumour, known in adults to be associated with the ectopic adrenocorticotrophic hormone syndrome, and the finding of adrenocorticotrophic hormone and related peptides in the tumour, confirmed the diagnosis of ectopic adrenocorticotrophic hormone secretion.

Serum adrenocorticotrophic hormone concentrations in pituitary dependent and ectopic adrenocorticotrophic hormone dependent hypercortisolism overlap, and dexamethasone responsive bronchial carcinoids have been reported in adults. Metyrapone in the dosage used produces a varying degree of block in patients with Cushing's syndrome. The block was incomplete in our patient. The very high values of cortisol derivatives found after the drug was given would usually be explained by the exaggerated pituitary adrenocorticotrophic hormone and cortisol response in patients with pituitary dependent disease resulting from a fall in circulating cortisol values in the first few hours of metyrapone administration.

Bronchial carcinoid tumours are rare in children, but as they may recur and metastasise a reliable tumour marker would be valuable. Although in this patient the pattern of adrenocorticotrophic hormone related peptides in plasma did not indicate the source of secretion, recent studies of adrenocorticotrophic hormone and related peptides in plasma and tumour tissue suggest that this may eventually permit more accurate aetiiological diagnosis of Cushing's syndrome and act as a tumour marker.

We thank Dr Betty Brownell and Mr H Coakham, Frenchay Hospital, Bristol and Professor Lesley Rees, St Bartholomew's Hospital, London, for the special investigations. PSW and MGM are supported by the Cancer and Leukaemia in Childhood Trust.

References

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Arthritis in cystic fibrosis

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SUMMARY We have confirmed previous observations of a transient, non-disabling recurrent arthritis in patients with cystic fibrosis. This arthritis differs from classic rheumatoid arthritis, is frequently associated with skin arthritis lesions, and its occurrence is unrelated to the severity of lung disease.

The association of a transient arthritis with cystic fibrosis was first reported by Newman and Ansell in 1979. We describe the clinical course and laboratory findings in 8 cystic fibrosis patients with acute arthritis not associated with pulmonary osteoarthritis.

Patients

The group comprised 6 girls and two boys aged 3 to 29 years (mean 13.5 years). The diagnosis of cystic fibrosis had been made on the basis of clinical and radiological findings, and raised sweat electrolyte measurements. At the onset of joint disease, pulmonary disease was mild in five patients, moderate in two, and advanced in one. Six patients were taking pancreatic enzyme preparations; five had Pseudomonas aeruginosa in their sputum cultures; and 6 were taking oral antibiotics continuously, two on a sporadic basis. Clubbing of varying severity was present in all patients, however, none had long bone pain or radiological evidence of periosteal elevation.
Cushing's syndrome and bronchial carcinoid tumour.

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