A mixed endocrine adrenal tumour causing steatorrhoea

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SUMMARY A 60 year old man developed steatorrhoea, weight loss, mild diabetes mellitus, labile hypertension and limb cramps. Raised plasma concentrations of catecholamines, particularly noradrenaline and a computed tomography-scan showing an adrenal tumour strongly suggested a pheochromocytoma. Adrenoreceptor blockade reversed the symptoms, decreased faecal fat, and increased duodenal trypsin to normal concentrations. After adrenalectomy the patient was asymptomatic and there was no steatorrhoea. The blood glucose concentrations became normal. Immunocytochemistry revealed the tumour cells to store large amounts of enkephalin and somatostatin reactive material and moderate amounts of immunoreactive β-endorphin and dynorphin.

The most common manifestations of pheochromocytoma are persistent or paroxysmal headache, sweating, palpitations, diabetes mellitus, weight loss, and hypermetabolism.1 Abdominal symptoms are usually not a major feature in pheochromocytoma, although nausea, vomiting, abdominal pain and less frequently, diarrhoea and gastrointestinal bleeding: as well as obstipation, megacolon and paralytic ileus,14 have been described. We know of no report in which malabsorption or significant steatorrhoea in patients with pheochromocytoma is described.

Somatostatin inhibits a variety of endocrine and exocrine functions. Patients with somatostatinoma often exhibit both steatorrhoea and mild diabetes mellitus.5 Although pheochromocytoma contain some somatostatin, opioid peptides and neuropeptide Y, adrenal tumours producing large amounts of these peptides giving rise to specific symptoms have not been described. In this paper we describe a patient with diabetes mellitus and significant steatorrhoea who had an adrenal tumour producing large amounts of noradrenaline, somatostatin, and opioid peptides.

Methods

FAT ABSORPTION

The triolein breath test was done as described previously.4 The peak expiratory 14CO2, expressed as per cent of given dose per hour, was used as a measure of fat absorption. Faecal fat was determined as described by van der Kamer et al.7 Urinary oxalate was determined by titration with permanganate,8 after giving 600 mg sodium oxalate daily for three days.

Table 1 Details of peptide antisera used

<table>
<thead>
<tr>
<th>Antigen</th>
<th>Code no</th>
<th>Immunofluorescence</th>
<th>Immuno-peroxidase</th>
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<tr>
<td>Met-enkephalin*</td>
<td>8107</td>
<td>1:320</td>
<td>1:640</td>
</tr>
<tr>
<td>Dynorphin†</td>
<td>8023</td>
<td>1:40</td>
<td>1:160</td>
</tr>
<tr>
<td>Rimorphin (dynorphin B)†</td>
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<td>1:40</td>
<td>1:160</td>
</tr>
<tr>
<td>β-endorphin</td>
<td>7762</td>
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<td>1:640</td>
</tr>
<tr>
<td>ACTH</td>
<td>1</td>
<td>1:80</td>
<td>1:320</td>
</tr>
<tr>
<td>Calcitonin</td>
<td>7714</td>
<td>1:160</td>
<td>1:640</td>
</tr>
</tbody>
</table>

*no cross-reaction with β-endorphin or dynorphin; †no cross-reaction with Me- or Le-enkephalin of β-endorphin; ‡no cross-reaction with enkephalin.
IMMUNOCYTOCHEMISTRY

Fresh tumour specimens were frozen in a mixture of propane and propylene, cooled to the temperature of liquid nitrogen, and freeze dried. They were then fixed by exposure to formaldehyde vapour for one hour at 80°C and embedded in paraffin in vacuo. Sections, mounted on albuminised slides were deparaffinised in xylene and hydrated. The sections were then processed for the immunocytochemical demonstration of various neurohormonal peptides known to occur in pheochromocytomas, as specified in Table 1, using the indirect immunofluorescence technique of Coons et al. Sections incubated with antiserum inactivated by the addition of antigen in excess (10–100 g of pure natural or synthetic peptide per ml diluted antiserum) were used as controls. Details of the peptide antisera used are given in Table 1.

Case report

A 60 year old man without any family history of diabetes or other endocrine disorder was admitted to the hospital in 1979 complaining of anorexia, loose stools and weight loss of approximately 5 kg over a few months. Physical examination was normal. Serum amino transferases and γ-glutamyl transferase were slightly raised. He had a mild steatorrhoea (Fig. 1) and a slightly lowered xylose absorption. No definite diagnosis was made and after a few months the symptoms disappeared, and the laboratory examinations including the analysis of faecal fat became normal.

He remained well for another three years and was then readmitted complaining of increasing volumes of loose, light coloured stools, loss of weight and disabling limb cramps and episodes of vertigo and sweating. Physical examination was normal but the patient now not only had marked steatorrhoea, with faecal fat 130 mmol/24 h (normal <17 mmol/24 h) but also a non-ketotic diabetes mellitus. Blood glucose concentrations were constantly raised and showed no correlation to meals. Blood cell counts, serum concentrations of enzymes, serum isoamylase, serum electrolytes and urine analysis were all normal. Ultrasonography of the liver, gall bladder and pancreas was normal but revealed an enlarged adrenal gland on the right side. Blood pressure was now regularly recorded and at times rose to 250/100 mm Hg. A computed tomography scan revealed a tumour (4–5 cm) at the site of the right adrenal gland.

Endoscopic retrograde cholangiopancreatography (Fig. 2) was normal. The concentration of trypsin in duodenal aspirate after a Lundh test meal was 75 μkat/l (normal >156 kat/l). Faecal fat was 124 mmol/24 h and urinary oxalate was raised (Fig. 1) C-peptide 0.46 nmol/l (0.25–0.75) and plasma insulin 4 mU/l (<25) were normal. Urine hydroxy-methoxy-mandelate was 81–85 mol/24 h (reference value 6–33 mol/24 h) and urine methoxycatechola-

Fig. 1 Determinations of faecal fat (□), and 14C-triolein breath test (■) at various times. Note the high value of peak expiratory 14CO2 before treatment.
amines 24–53 mmol/24 h (reference value 0.6–6.0 mol/24 h). During α-adrenergic blockade with phenoxybenzamine, faecal fat decreased to 44 mmol/d and after the operation it decreased further to normal values. The 14C-triolein breath test gave contrasting results. The peak expiratory 14C was normal initially but was low after α-adrenoceptor blockade, when fat absorption was improved according to faecal fat measurements. After the operation the triolein breath test was normal. It is possible that the breath test overestimated the degree of fat absorption before the α-adrenoceptor blockade because of the stimulatory effect of the catecholamines on fatty acid oxidation.

Immunocytochemistry revealed that the vast majority of tumour cells displayed intense enkephalin and somatostatin immunoreactivity. Immunostaining of consecutive sections for the two peptides showed that both occurred in the same cells. In addition, single scattered or clustered cells displayed dynorphin of β-endorphin immunoreactivity. No immunostaining was obtained using ACTH or calcitonin antisera.

The tumour also seems to have produced multiple opioid peptides. The immunocytochemically identified opioids in the tumour consisted enkephalins, dynorphins and β-endorphin. There is recent evidence that all these peptides may occur not only in pheochromocytomas but also in the normal human adrenal medulla. The clinical significance of the production (and presumable secretion) of opioid peptides and somatostatin in pheochromocytomas is obscure.

The steatorrhoea decreased after α-adrenoceptor blockade indicating that the catecholamines contributed to the patients symptoms. The increase in the duodenal trypsin concentrations after the blockade suggests that suppression of exocrine
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pancreatic secretion by catecholamines\textsuperscript{12} may be one factor contributing to the steatorrhoea. Faecal fat excretion was, however, not normal until after operation and reversible diabetes mellitus and steatorrhoea are also features of the somatostatinoma syndrome.\textsuperscript{5} Possible effects of the somatostatin and the opioid peptides present in the tumour have to be considered. The mechanisms by which this tumour induced steatorrhoea and reversible diabetes mellitus therefore remains unknown.

References