A mixed endocrine adrenal tumour causing steatorrhoea

P THESLEFF, C BENONI, H MÅRTENSSON, Å NILSSON, F SUNDLER, AND B ÅKESSON

From the Departments of Internal Medicine, Surgery, Histology and Clinical Chemistry, University of Lund, Lund, Sweden

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,² as well as obstipation, megacolon and paralytic ileus,^{3,4} 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.⁶ The peak expiratory $^{14}\text{CO}_2$, 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

Antigen	Code no	Working dilution	
		Immuno-fluorescence	Immuno-peroxidase
Met-enkephalin*	8107	1:320	1:640
Dynorphin†	8023	1:40	1:160
Rimorphin (dynorphin B)‡	8329	1:40	1:160
β -endorphin	7762	1:80	1:640
ACTH	1	1:80	1:320
Calcitonin	7714	1:160	1:640

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

Address for correspondence: Dr Peter Thesleff, Department of Internal Medicine, University Hospital of Lund, S-221 85 Lund, Sweden.

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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*.⁹ 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.*¹⁰ 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 μ kat/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 mIU/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 ($\square$), and ^{14}C -triolein breath test (hatched) at various times. Note the high value of peak expiratory $^{14}\text{C}_2$ before treatment.

Fig. 2 Immunofluorescence micrographs of sections from the same tumour region using antisera against Met-enkephalin (top) and somatostatin (below). Virtually all tumour cells are stained with each of the antisera implying coexistence of immunoreactive enkephalin and somatostatin in the cells of this tumour.

mines 24–53 mol/24 h (reference value 0.6–6.0 mol/24 h). During α -adrenoceptor blockade with phenoxybenzamine (Dibenylene 20–60 mg per day for seven weeks) coeliac angiography was carried out. This showed a highly vascularised tumour. Selective venous sampling from the adrenal veins showed markedly raised concentrations of noradrenaline on the right side. Percutaneous transhepatic portography with selective sampling showed normal concentrations of serum pancreatic polypeptide. During the α -adrenoceptor blockade there was a dramatic improvement: the diarrhoea and abdominal cramps disappeared. Faecal fat and urinary oxalate decreased markedly and trypsin in duodenal content was increased. The patient underwent adrenalectomy during α -adrenoceptor blockade. At operation a 5×5 cm encapsulated tumour was found in the right adrenal gland. This was removed without any technical problem. The left adrenal gland and the pancreas were normal. After the operation the patient has remained free of symptoms, and with no sign of diabetes mellitus. His blood pressure has been normal. Laboratory tests are summarised in Table 2.

Table 2 Summary of test results

	Before treatment	During α -adrenoceptor blockade	After adrenalectomy
Faecal fat	124	44	8
Duodenal trypsin	75	175	249
C-triolein test	5.08	0.74	6.46
Urine oxalate	0.35	0.18	0.19

Faecal fat (<17 nmol/24 h); trypsin in duodenal aspirate after Lundhs test meal (>156 *ukat/l*); ^{14}C -triolein test, maximal CO_2 -excretion after ^{14}C -triolein load (preliminary reference values 3.3–7.5%/h); urine oxalate after sodium oxalate load (0.24 mmol/l).

Results and Discussion

The patient had a marked fat malabsorption with faecal excretion of between 130 and 77 mmol/d (Fig. 1). After α -adrenergic blockade with phenoxybenzamine, faecal fat decreased to 44 mmol/d and after the operation it decreased further to normal values. The ^{14}C triolein breath test gave contrasting results. The peak expiratory $^{14}\text{CO}_2$ 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 or 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 comprised 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.¹¹ 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

pancreatic secretion by catecholamines¹² 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.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.

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