Diabetes mellitus after hypophysectomy for acromegaly

Insulin resistance, glucose intolerance, and diabetes are associated with acromegaly and resolve or improve after treatment. 1 2 We describe three patients who paradoxically developed diabetes mellitus soon after hypophysectomy for acromegaly.

Case reports

CASE 1

A 25 year old woman presented with symptoms suggestive of acromegaly; plasma glucose concentration was 5-4 mmol/l (table) and serum human growth hormone concentration >125 mU/l. Computed tomography showed an enlarged sella turcica and a pituitary tumour with suprasellar extension. Intravenous insulin (0-1 IU/kg) caused hypoglycaemia during a stress test. Four days after transfrontal hypophysectomy she developed hyperglycaemia (plasma glucose concentration 11-25 mmol/l). She was treated with insulin and hydrocortisone (30 mg daily).

Four months later she was admitted with diabetic ketoacidosis and staphylococcal septicemia. Intravenous insulin (up to 20 IU/h) was given for several days to control her diabetes. An insulin stress test (0-5 IU intravenous insulin/kg) did not result in hypoglycaemia. Serum human growth hormone concentration was 48 mU/l. She was discharged taking insulin, replacement hydrocortisone and bromocriptine. Her serum human growth hormone concentration fell to 7-5 mU/l over six months, and she had episodic hyperglycaemia. Insulin was stopped without recurrence of diabetes.

CASE 2

A 35 year old woman presented with features of acromegaly and an enlarged sella turcica. Serum human growth hormone concentration was >160 mU/l. A 75 g glucose tolerance test yielded normal results. Four weeks after transsphenoidal hypophysectomy polyuric and polydipsia occurred; plasma glucose concentration was 20 mmol/l, haemoglobin A1c 12%, and human growth hormone 100 mU/l. She was treated with glibenclamide, given external pituitary irradiation, and started on bromocriptine (15 mg daily). Serum human growth hormone concentration fell to 30 mU/l. Eight weeks later she developed hypoglycaemic episodes and glibenclamide was stopped. Fasting glucose, haemoglobin A1c and human growth hormone concentrations remained normal with bromocriptine treatment (table).

CASE 3

A 36 year old woman presented with acromegaly. Fasting plasma glucose concentration was 5-5 mmol/l (table) and human growth hormone concentration >160 mU/l. Computerized tomography showed a pituitary mass extending into the left temporal lobe, which was partly removed at craniotomy. Five days postoperatively her plasma glucose concentration rose to 21-3 mmol/l. She was treated with insulin until she became normoglycaemic 10 days later. External irradiation of the tumour was performed. Over the next 12 months her fasting plasma glucose concentration ranged from 5 to 8 mmol/l. Her human growth hormone concentration fell gradually (49 and 21 mU/l at six and 12 months after operation).

She developed symptomatic diabetes 16 months after operation (plasma glucose concentration 18-4 mmol/l) and had a serum human growth hormone concentration of 78 mU/l. She was treated with insulin. After bromocriptide 5 mg daily was added her treatment her diabetes could be controlled with glibenclamide, which was finally withdrawn as her human growth hormone concentration fell to 40 mU/l.

Comment

These three patients had large tumours secreting human growth hormone with suprasellar extensions and considerably increased serum human growth hormone concentrations. They had normal glucose tolerance and insulin sensitivity on presentation and no family history of diabetes. After hypophysectomy human growth hormone concentrations fell in all three patients (although they were still supranormal) but diabetes developed rapidly. This suggests that there may be a causal relation between hypophysectomy and diabetes in patients with acromegaly. Hypophysectomy and bromocriptine treatment in patients with acromegaly are associated with an improvement in, and the resolution of, diabetes and glucose intolerance respectively. 1 2

Although the mechanism underlying the pathogenesis of diabetes with falling human growth hormone concentrations in these patients is not clear, the possible mechanisms are (a) a biphasic effect of the human growth hormone, with an anti-insulin effect at moderately high concentrations and an effect similar to that of insulin at extremely high concentrations; this phenomenon has been previously shown in vitro 3 and in vivo; and (b) mechanical or ischaemic injury of the brain stem by the tumour or surgery, or both.

Effect of the pollen season on nasal mast cells

The number of pollen grains necessary to produce rhinitis in patients with hay fever decreases as the pollen season progresses—a phenomenon known as nasal priming and usually attributed to an increase in the non-specific reactivity of the nasal mucosa. A similar effect could result from an increase, particularly in the superficial epithelial cell layer, in the number of mast cells sensitised by specific immunoglobulin E against grass pollen. We studied the effect of the pollen season on the total number of mast cells in the nasal mucous membrane and the proportion present in the epithelium.

Subjects, methods, and results

Eight volunteers (six women, two men; mean age 32) all had at least a five year history of rhinitis during only the grass pollen season. The results of skin prick tests were positive (weal >3 mm) with group B, mixed grass pollen 2-5% weight/volume and negative with Dermatophagoides pteronyssinus 1-2% weight/volume (Bencard, Brentford, United Kingdom). They did not take any drugs for their rhinitis during the grass pollen season (May-August). Informed consent was obtained from all volunteers for this study, which had the approval of the district ethical committee.

Nasal biopsy samples about 4 mm in size were obtained from the inferior turbinate with modified Grünwald punch biopsy forceps five minutes after the topical application of 10% xylocaine. Samples were obtained from all volunteers in July 1985 at the height of the grass pollen season, in October after the season, and in January 1986 in midwinter. The coded biopsy samples were fixed in Carnoy’s solution and stained with α-naphthol AS-D chloroacetate esterase stain (Sigma). The area of the whole section was measured by planimetry. Each mast cell was counted and the number of mast cells per mm³ of nasal tissue calculated.

Statistical analysis was by Wilcoxon’s signed rank test and Student’s paired t test.

The table shows the total number of mast cells per mm³ of nasal mucous membrane for each of the volunteers in July, October, and January. Not only was there an increase in the total numbers of mast cells in both the epithelium and the lamina propria in July 1985 compared with October but there was also a significant increase in the proportion of mast cells present in the epithelium in July 1985 compared with January 1986 (p<0.05).

Comment

The results of this study show that there was an eightfold increase in the number of mast cells in the nasal mucous membrane of patients with seasonal allergic rhinitis in the summer compared with that during the winter months and that the proportion of cells in the surface epithelial layer increased fourfold. As our patients suffered from symptoms during only the grass pollen season these changes in the number and site of the mast cells were probably related to natural exposure to the allergen. Recently, Enerbäck et al showed migration of mast cells to the nasal epithelium during the birch pollen season in Scandinavia but did not find an increase in the total number of mast cells in the nasal mucous membrane at the height of the pollen season. Mast cells are rarely, if ever, found in the epithelium of patients who do not have rhinitis, but the total number in the nasal mucous membrane is similar to that in patients with seasonal allergic rhinitis outside the pollen season. Treatment that prevents the accumulation of mast cells in the nasal epithelium could be effective in treating allergic rhinitis as higher pollen counts would probably be required to trigger symptoms. Indeed, the results of recent studies of human skin have shown that potent topical corticosteroids can cause a depletion in the number of mast cells, and intranasal corticosteroids, which are effective in treating allergic rhinitis, may act in this way.

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