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Cardiomegaly and heart failure in a patient with prolactin-secreting pituitary tumour

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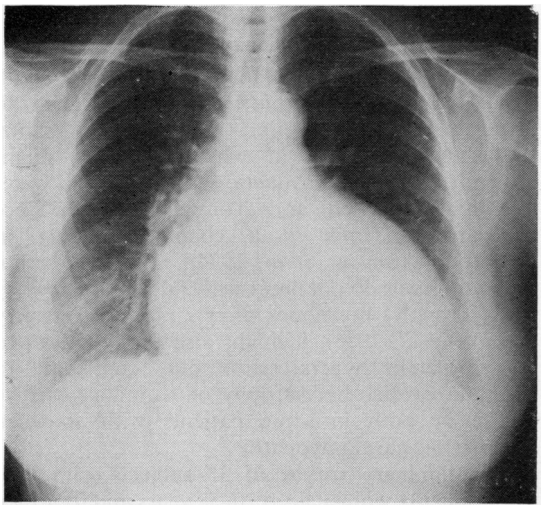
ABSTRACT Unexplained cardiomegaly with cardiac failure was observed in a 42-year-old woman in whom a pituitary tumour had been treated by radiotherapy five years previously. She had been amenorrhoeic for 10 years. Thyroid and adrenal function was normal. Despite treatment with digitalis and diuretic, her cardiac disease progressed until she died suddenly at the age of 45. Hyperprolactinaemia was evident some weeks before death, her serum concentration of 68 ng/ml being well above both the reported normal range (2–20 ng/ml) and the concentrations in eight female controls being treated for severe cardiac failure (5–25 ng/ml). Although the association of these two disorders might merely represent coincidence, heart disease with similar features is common in acromegaly and does not correlate with plasma growth hormone concentration. Since prolactin is known to exert metabolic growth hormone-like effects in animals and in man, the possibility should be considered that prolactin hypersecretion might induce or maintain cardiac disease in some patients with pituitary tumours. A preliminary survey of 35 subjects with hyperprolactinaemia has shown five with raised blood pressure and four, two of whom were normotensive, with cardiomegaly on chest radiographs.

Cardiomegaly is an almost uniform finding in acromegalic patients (Daughaday, 1968). Cardiovascular disorders have often been associated with acromegaly (see McGuffin *et al*, 1974, for review) and represent the main cause of death in this disease (Wright *et al*, 1970). Though in most cases known aetiological factors of heart disease, such as hypertension, diabetes mellitus, coronary atherosclerosis, or sometimes hyperthyroidism, had been present, patients with unexplained cardiomyopathy have been described (McGuffin *et al*, 1974), and the existence of a specific acromegalic cardiomyopathy has been suggested (Pepine and Aloia, 1970; Joplin and Lewis, 1973). The incidence of cardiac failure, however, has been reported to increase rather than decrease after effective treatment of acromegaly (Hamwi *et al*, 1960), and a prospective study has failed to show any correlation between the plasma growth hormone concentration and the existence of cardiac disease (McGuffin *et al*, 1974). This has led to speculation that the cardiovascular complications of acromegaly might be due to other pituitary products (Cavalieri, 1975). We report a case of unexplained cardiomegaly and heart failure associated with prolactin hypersecretion by a pituitary tumour.

Case report

A 42-year-old white woman was admitted to the hospital in February 1974 because of dyspnoea on exertion, paroxysmal nocturnal dyspnoea, and ankle oedema for two months. Menarche had occurred at the age of 16 and the patient had been oligomenorrhoeic since then. She married at the age of 28 but never became pregnant. From the age of 32 the patient had been amenorrhoeic. In the next 10 years she noticed weight gain of some 30 kg and complained of headache of progressively increasing severity. When aged 37 pituitary tumour was diagnosed by air encephalography, and she was treated with telecobalt treatment with remission of her headache. No visual field impairment had occurred either before or after treatment, and she had been well until two months before admission. She was overweight (height 153 cm, weight 69 kg) but not dyspnoeic at rest; pulse was 88, regular and blood pressure 140/80 mmHg; the liver was palpable 3 cm below the costal margin, and there was ankle oedema. There was no galactorrhoea. A chest radiograph showed massive cardiac enlargement and pulmonary stasis (see figure). The electrocardiogram suggested moderate left ventricular hypertrophy and



Chest radiograph of patient on first hospital admission.

showed ST-T changes in left ventricular leads; isolated ventricular ectopic beats were also present. A skull radiograph confirmed the existence of an enlarged sella with a very thin dorsum. Endocrinological evaluation showed normal serum thyroxine (6·1 μg/100 ml) and resin triiodothyronine uptake as evaluated by a competitive protein binding radioassay, a slightly raised ^{131}I thyroid uptake (9, 22, and 54, and 67% at 2, 6, 24, and 48 h respectively) with a normal $PB^{131}I$ (0·09% of the administered dose per litre of plasma) and thyroid scintiscan. Serum radioimmunoassayable thyrotrophin was normal at 1·4 μU/ml with a peak of 29·3 μU/ml and a slow decline after intravenous injection of thyrotrophin-releasing hormone (200 μg). Plasma fluorogenic corticosteroids (10·4 μg/100 ml) and urinary Porter-Silber chromogens (3·8 mg/24 h) were also normal. Serum growth hormone was normal at 0·8 ng/ml and did not increase above this level during a four-hour oral glucose tolerance test. Serum gonadotrophins were within the normal range (follicle-stimulating hormone, 14·1 mIU/ml; luteinising hormone, 25 mIU/ml). Serum prolactin determination was not available in this institution at that time. Oral glucose tolerance, serum cholesterol, triglycerides, sodium, potassium, calcium, phosphorus, urea nitrogen, and creatinine were normal. Cardiomyopathy was suggested on cardiac catheterisation by finding raised wedge pressure and left ventricular end-diastolic pressure with no valvular gradients or shunts. She was discharged from the hospital and started digoxin and frusemide treatment. In May 1975, having been relatively well for over a year, she was again admitted because high blood pressure had been discovered during a follow-up visit. Her blood pressure was now 150/120 mmHg; physical examination found no signs of cardiac failure. On the following days in hospital blood pressure was recorded as 140/95 mmHg or less. Renal function was normal as judged by serum chemistry, glomerular filtration rate, and radioisotope renogram; plasma renin activity was normal at 1·14 ng/ml/h. The electrocardiogram showed worsened signs of left ventricular hypertrophy and ST-T changes with inverted T waves in left ventricular leads. Her heart was no larger than on the first hospital admission. When discharged she was taking digoxin and frusemide and she remained well until January 1977, when she complained again of dyspnoea on exertion and at rest. Chest radiograph showed further cardiac enlargement with left cardiac profile at the chest wall. In March 1977 she was admitted with pulmonary oedema and was treated with ouabain and frusemide. Blood pressure was 140/90 mmHg. The electrocardiogram showed worsened signs of coronary insufficiency. After eight days in hospital the patient was relatively well on digoxin and frusemide. Blood was taken next morning for hormonal determinations and she was discharged. In April 1977 she died suddenly at home: necropsy was not performed.

On the last admission, serum thyroxine was 4·4 μg/100 ml (normal, 3·5–12·5), resin triiodothyronine uptake was 98·7% (normal, 92–117), and free thyroxine index was 4·46 (normal, 3·5–12·5); serum triiodothyronine was 120 ng/100 ml (normal, 70–180); serum thyrotrophin was 5·9 μU/ml (normal, <1–4·5); serum growth hormone was 1·8 ng/ml (normal, <1–5); and serum prolactin was 68 ng/ml (mean of two samples taken at 30 minute-interval; normal values, 2–20 ng/ml). The mean serum prolactin concentration in eight women with pulmonary oedema treated with ouabain and frusemide who were studied as controls was 10·7 ng/ml (range, 5–25 ng/ml).

Discussion

The case history of this patient resembles very closely some reported cases of acromegalic heart disease (Pepine and Aloia, 1970; Joplin and Lewis, 1973; McGuffin *et al*, 1974). While it is interesting that cardiac decompensation has been reported in patients with very mild acromegaly and in patients in whom growth hormone secretion had been normalised or even impaired by successful treatment (Hamwi *et al*, 1960; Joplin and Lewis, 1973; McGuffin *et al*, 1974), our patient had no history or clinical features of acromegaly, and her serum growth hormone concentration was re-

peatedly normal when she came to our attention. She had been oligomenorrhoeic and infertile until the age of 32, when she became amenorrhoeic; subsequently, suggestive symptoms of intracranial hypertension led to the diagnosis of pituitary tumour. Five years after successful radiotherapy she developed cardiac failure. One year later she presented with moderate and unstable hypertension. Two years later hyperprolactinaemia was finally, though tardily, found. The raised prolactin concentrations found in the patient do not seem to be related to stress factors or to drug treatment, since the serum prolactin concentration did not exceed 25 ng/ml in eight women with severe circulatory failure studied as controls during treatment with ouabain and frusemide. Since hyperprolactinaemia is common in patients with "functionless" pituitary tumours (Snyder *et al*, 1974), especially in women presenting with hypogonadism without other endocrine dysfunction (Child *et al*, 1975), the patient probably had long-standing prolactin hypersecretion from a pituitary tumour, which was maintained after radiotherapy either by residual adenomatous cells or by interference with the hypothalamic inhibitory control mechanism of prolactin secretion. The patient had no known aetiological factors of heart disease, including rheumatic disease, hypertension, thyrotoxicosis or hypothyroidism, diabetes mellitus, hyperlipidaemia, smoking, or alcohol consumption.

The coexistence of hyperprolactinaemia and heart disease in this woman might merely represent coincidence, since such an association has not previously been recognised. Detailed studies, however, of the cardiovascular system in functionless pituitary tumours have not been reported, and serum prolactin determination has only recently become available. The possibility that prolactin hypersecretion might lead to heart disease must therefore be considered. Prolactin is structurally closely related to growth hormone (Wallis and Davies, 1976), possesses growth-promoting activity in animals (Nicoll and Bern, 1972), and exerts growth hormone-like metabolic effects in man, including nitrogen retention, increased calcium excretion, impairment of glucose tolerance, fat mobilisation, and even skeletal growth (McGarry and Beck, 1972; Berle *et al*, 1974; Landgraf *et al*, 1977). Moreover, growth hormone and prolactin bind to one common receptor in rat liver cell membranes (Posner *et al*, 1974) and in human lymphocytes (Lesniak *et al*, 1977); somatomedin generation has been found in rat liver after perfusion with ovine prolactin (Francis and Hill, 1975); prolactin has been shown to increase serum somatomedin-like activity and to promote growth in hypopituitary dwarf mice (Holder and Wallis, 1977). Cardiomyopathy (MacDonald *et al*, 1972) and sudden death (Leestma and Koenig, 1968) have been reported in some patients on chronic treatment with large doses of phenothiazines, drugs known to stimulate prolactin secretion (Kleinberg and Frantz, 1971). Another way in which prolactin might disturb cardiovascular function is sodium and water retention (Hanssen and Torjesen, 1977). Since hyperprolactinaemia is a common finding in acromegaly (Snyder *et al*, 1974), and since serum prolactin levels do not necessarily fall simultaneously with growth hormone after pituitary surgery (Franks *et al*, 1976), it might also be hypothesised that prolactin hypersecretion may contribute to maintain cardiac hypertrophy or to induce cardiac failure or both in some patients with so-called acromegalic cardiomyopathy.

A preliminary survey of 35 subjects with prolactinoma (31 women aged 20–58 years and four men aged 30–42 years) admitted to the department of neurosurgery of the University of Milan showed the existence of raised blood pressure levels (systolic values greater than 160, diastolic greater than 95 mmHg) in five cases (four women aged 24–50 and one man aged 39); cardiomegaly was found on the chest radiographs of the two patients who had diastolic blood pressure levels greater than 110 mmHg (a woman aged 41 and a man aged 39) and in two normotensive women aged 30 and 58 who had had symptoms suggestive of a pituitary tumour for 15 and 24 years respectively. Although the prevalence of hypertension in these patients may thus not differ from that found in the general population, the finding of cardiomegaly in the absence of any known aetiological factors of heart disease in some patients with long-standing prolactinoma is of interest, especially as the mean duration of pituitary disease in the entire series was estimated to be only $6{\cdot}8 \pm 0{\cdot}9$ (SE) years by the time the first endocrine or neurological symptoms occurred. Prospective studies are obviously needed to evaluate the incidence of heart disease in hyperprolactinaemic subjects and the possible role of prolactin in the pathogenesis of cardiovascular disorders associated with pituitary tumours.

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