A practical approach to the investigation of the hyperprolactinaemic patient

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Summary
Pituitary function was assessed in 39 patients with previously untreated hyperprolactinaemia. Primary hypothyroidism, drug-induced hyperprolactinaemia and chronic renal failure were excluded in all patients. All of the 22 patients (group 1), who had either a normal pituitary fossa or a minor radiological change on lateral skull X-ray, had completely normal pituitary function with the exception of 2 who were partially growth hormone-deficient. However, 9 of the 17 patients with macroadenomas (group 2) had a deficit of one or more anterior pituitary hormones. After the lateral skull X-ray 13 patients in group 1 had further neuroradiological investigations. In only one was a minor abnormality noted which had not been observed on the plain film and this was of no practical significance.

In centres where hyperprolactinaemic patients with a normal pituitary fossa or a minor radiological change on lateral skull X-ray are treated with bromocriptine, further neuroradiological investigations and dynamic tests of pituitary function are not required.

Introduction
The main pathological causes of hyperprolactinaemia are pituitary adenomas, hypothalamic disease, primary hypothyroidism, drugs, chronic renal failure and unknown (functional or idiopathic hyperprolactinaemia). Once primary hypothyroidism and drug causes are excluded, the major differential diagnosis lies between a pituitary adenoma and functional hyperprolactinaemia, which may itself be due to the presence of a prolactin-secreting microadenoma. For such patients, many authorities (Jacobs 1976; Vezina and Sutton, 1974; Marrs et al., 1979) recommend tomography of the pituitary fossa, and further biochemical investigations may include dynamic tests of prolactin secretion (Cowden et al., 1979; Boyd, Reichlin and Turksoy, 1977) and anterior pituitary function. The present authors believe that the type and extent of both the radiological and biochemical investigations should depend upon the radiological appearances of the pituitary fossa in the lateral skull X-ray and the local availability of different types of therapy for treating hyperprolactinaemia. This view is based on their results in 39 previously untreated hyperprolactinaemic patients investigated in their unit over the last 4 years.

Patients and methods
Thirty-seven women, whose ages ranged from 17 to 58 (mean 32.1) years, and 2 men, aged 23 and 33 years, were studied. In each patient the basal serum prolactin concentration, estimated on at least 2 occasions, exceeded 600 mu./l. The mean basal serum prolactin concentration for each patient is shown in Fig. 1. Eight of the patients were acromegalic and their primary symptoms were headaches, excess sweating and arthralgia. Of the remaining 31 patients, 30 were premenopausal females, 19 were amenorrhoeic, 7 oligomenorrhoeic and one was infertile with regular menses. Galactorhoea was present in 16 of the 39 patients. Primary hypothyroidism, drug causes and chronic renal failure were excluded in all patients. Visual fields were assessed by perimetry.

Pituitary function and reserve were assessed in all patients by a combined i.v. infusion of thyrotrophin-releasing hormone (TRH 200 μg), luteinizing hormone releasing hormone (LHRH 100 μg) and insulin (0.2 u./kg). Blood samples were taken at 0, 20, 30, 60, 90 and 120 min. Responses of thyroid stimulating hormone (TSH), luteinizing hormone (LH), follicle stimulating hormone (FSH), growth hormone (GH) and cortisol were noted. In normal subjects, the peak GH and cortisol responses after insulin hypoglycaemia are >20 μu./l and >500 nmol/l respectively. The serum triiodothyronine (T₃) (normal range 1.2–2.8 nmol/l) and serum thyroxine (T₄) (normal range 50–150 nmol/l) were measured in the basal sample. The basal serum TSH in normals is less than 6 μu./l and 1 μu./l with a TSH increment after TRH which ranges from 4 to 24 μu./l. In the premenopausal female controls the basal serum FSH and LH concentrations ranged from 2 to 9 μu./ml and the increment after LHRH from 4 to 7 μu./ml for FSH and 4 to 25 μu./ml for LH respectively during the mid-follicular phase. In postmenopausal females, the basal serum FSH concentration is...
FSH, is measured by immunoassays (Shalet et al., 1975). Plasma cortisol was measured fluorimetrically (Mattingly, 1962). Serum prolactin was also estimated by radioimmunoassay, initially using the supraregional assay service (MRC standard 71/222) but latterly, from February 1979, it was measured locally (NIBSC standard 75/504).

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\geq 20 \text{ mu./ml and the basal serum LH concentration is } \geq 15 \text{ mu./ml. Serum concentrations of TSH, T}_3, T_4, \text{ FSH, LH and GH were measured by radioimmunoassays (Shalet et al., 1975). Plasma cortisol was measured fluorimetrically (Mattingly, 1962). Serum prolactin was also estimated by radioimmunoassay, initially using the supraregional assay service (MRC standard 71/222) but latterly, from February 1979, it was measured locally (NIBSC standard 75/504).}
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Results

In group 1 no patient had any visual field loss. In one patient, in whom the pituitary fossa had been described as normal on the lateral skull X-ray, tomography of the pituitary fossa suggested that there was a one-mm asymmetry between the right and left sides of the floor of the pituitary fossa. The further neuroradiological investigations in the other 12 patients in group 1 revealed no abnormality and were consistent with the normal appearance of the pituitary fossa seen on lateral skull X-ray.

All 22 patients in group 1 had normal serum TSH, T_3 and T_4 concentrations with a normal TSH response to TRH and a normal cortisol response to insulin hypoglycaemia. All but 2 patients showed a normal GH response to insulin hypoglycaemia. Twelve of the group were amenorrhoeic and in the premenopausal age range; none showed evidence of gonadotrophin deficiency and 6 have subsequently become pregnant on treatment with bromocriptine. One female in group 1 was 53 years old and her basal gonadotrophin concentrations were in the postmenopausal range. The basal gonadotrophin concentrations and gonadotrophin responses to LHRH in the remaining 9 patients were normal.

Two patients in group 2 showed partial visual field loss; the neuroradiological investigations, however, revealed evidence of suprasellar extension of a macroadenoma in 6 patients.

Seven of the 17 patients in group 2 were acromegalic which meant that the function of the normal somatotrophic cells could not be assessed, but 6 of the remaining 10 were GH-deficient. Six out of the 17 were gonadotrophin-deficient and one of these was also ACTH-deficient; no others were ACTH-deficient and none was TSH-deficient. The gonadotrophin deficiency was diagnosed by low normal basal gonadotrophin concentrations and blunted gonadotrophin responses to LHRH which did not alter after normoprolactinaemia had been restored with bromocriptine.

Discussion

Hyperprolactinaemia in patients with a normal pituitary fossa on X-ray, and without an obvious cause, is often labelled functional, with the implication that no pituitary tumour is present. There are difficulties in this view since surgery has sometimes revealed small microadenomas (Cowden et al., 1979). The 2 major therapeutic approaches, in these patients and those with radiologically-defined microadenomas, have been selective adenomectomy or bromocriptine. A variety of dynamic tests of prolactin release have been described with the object of predicting whether a prolactin-secreting microadenoma is present or not. The hypothesis being that, in the absence of a pituitary tumour, the
responses to stimulation are normal and if they are not then a pituitary tumour can safely be diagnosed even if fossa X-rays are normal. The knowledge that a microadenoma is present is obviously of great importance to the neurosurgeon, but the authors choose, like many others, to treat these patients (group 1) with bromocriptine. This therapy is effective whether or not a small tumour is present (Jacobs, 1976). Furthermore, some prolactinomas clearly respond to these stimulation tests (Boyd et al., 1977; Jacobs et al., 1976). Therefore they do not perform any tests of prolactin release in their hyperprolactinaemic patients.

Klijn et al. (1980) showed that in hyperprolactinaemic patients the size of a pituitary tumour was critical in determining whether or not pituitary hormonal deficiencies developed. The present data lend strong support to this view as only 2 out of 22 patients with microadenomas or functional hyperprolactinaemia (group 1) showed any pituitary hormonal deficiency whereas 9 out of 17 patients with macroadenomas had a deficit of one or more anterior pituitary hormones. The 2 patients with abnormal results in group 1 both showed evidence of partial GH deficiency, but no patient in this group showed evidence of gonadotrophin, TSH or ACTH deficiency which would be of practical significance. In view of these results, the authors no longer routinely perform insulin tolerance tests, TRH and LHRH tests in patients with hyperprolactinaemia and an X-ray of the pituitary fossa which is either normal or shows a minor radiological change.

It has been proposed (Jacobs, 1976; Vezina and Sutton, 1974; Marrs et al., 1979) that sella tomography should be performed in all patients with hyperprolactinaemia. This suggestion has been supported on 2 grounds: firstly, microadenomas may cause minor radiological changes which may be missed on a single lateral film of the pituitary fossa but detected by tomography; secondly it is very important to diagnose pituitary tumours, however small, in these patients, as these tumours may expand during any subsequent pregnancy and potentially threaten the vision of the patient.

Minor radiological abnormalities of the pituitary fossa are very difficult to interpret as some authorities (Swanson and Du Boulay, 1975) believe they are an extremely common finding in normal subjects. Furthermore the experience of the radiologist is likely to be an important factor in determining how often minor but significant radiological changes are detected by tomography but not by a plain lateral film of the pituitary fossa. In the present study only one out of 7 patients with a normal pituitary fossa on the plain film showed any abnormality with tomography. Marrs et al., (1979) found 7 out of 87 patients with hyperprolactinaemia and a normal plain film had an abnormal tomogram. Therefore, the yield of abnormal tomograms in patients with normal plain films is small, i.e. 8%, and the cause of the minor radiological abnormality in these patients is not necessarily a microadenoma. Furthermore, the amount of radiation exposure to the lens of the eyes is considerably increased if tomography is performed (Chin, Anderson and Gilbertson, 1970).

In previously untreated females with prolactin-secreting microadenoma Gemzell and Wang (1979) reported that 94.5% of 91 patients subsequently underwent an uncomplicated pregnancy. Of the 5 patients (5.5%) who did develop complications during pregnancy, 4 were managed conservatively.

For these reasons, the authors no longer routinely perform pituitary tomography in hyperprolactinaemic patients with a normal plain film of the pituitary fossa. In addition, the treatment offered to these patients or to those with minor radiological changes is the same, i.e. bromocriptine. Once pregnant, the patients in both these groups are advised to report headaches or visual deterioration immediately and the visual fields are checked monthly.

References


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