patients with pituitary adenomas secreting prolactin. Data obtained after longer follow up are obviously required, but our early results over five years using this approach are more encouraging than those of other groups.6 10

References

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Treatment of presumed prolactinoma by transsphenoidal operation: early and late results

J A THOMSON, G M TEASDALE, D GORDON, D C McCRUDBEN, D L DAVIES

Abstract

Seventy seven patients who were presumed to have a prolactinoma on the basis of biochemical findings underwent transsphenoidal operation between October 1977 and September 1983. Sixty one patients were found to have a microadenoma, and hyperprolactinaemia was cured in 46 of these, amenorrhoea in 39 (80% of those with the symptom), galactorrhea in 32 (80%), and infertility in 31 (82%). Four of eight patients found to have a macroadenoma were also satisfactorily treated with surgery. Two patients had a lession other than a prolactinoma, and in six a tumour could not be found at operation; four of these last eight patients had a normal serum prolactin concentration after operation. Recurrent hyperprolactinaemia was rare, occurring in only three patients in the series overall; among the 32 patients followed up for more than five years only two of the 22 whose operation had initially been successful developed recurrent hyperprolactinaemia.

Introduction

An operation on the pituitary is now widely accepted as the best method of treating acromegaly and Cushing’s disease, but the management of tumours producing prolactin remains controversial. Series reported from Britain have concentrated on radiotherapy and treatment with dopamine agonists such as bromocriptine; surgery has to some extent been neglected and sometimes misrepresented.1 2

We have treated a consecutive series of 77 patients with hyperprolactinaemia by transsphenoidal operation. We have previously reported the laboratory diagnosis of prolactinoma,3 the radiological findings,4 the initial results of operation in the first 14 patients, the restoration of fertility and the outcome of pregnancy,5 and the factors affecting prognosis.6 This report provides an overview of the clinical and biochemical results and pays special attention to the long term outcome.

Methods

The patients included in this review each presented with amenorrhoea, galactorrhea, or infertility. Each had a serum prolactin concentration that was persistently above normal and impaired responses to dynamic testing with thyrotrophin releasing hormone or metoclopramide.7 The serum prolactin concentration was estimated using a radioimmunoassay; the coefficient of variance of the assay was 5% within batches and 10% between batches, and our normal reference range for serum prolactin concentration was 60-360 mU/l.8

Radiological investigation evolved during the years of the study. In each patient a plain x ray film of the skull was obtained, usually coupled with tomograms of the pituitary fossa. Each patient also underwent computed tomography. Orbital phlebography was used routinely to display the venous and arterial relations of the pituitary gland.9 Carotid angiography and metrizamide cisternography and ventriculography10 were used selectively to clarify detailed anatomical abnormalities and were needed in only seven and
eight patients, respectively. Dopamine agonists were used before operation by only 16 patients (11 with a microprolactinoma, four with a macroprolactinoma, and one in whom a prolactinoma was not found).

Operation was carried out by a transsphenoidal microsurgical technique. When a tumour was found in a 1-2 mm rim of tissue at its interface with the normal gland it was also removed. Preoperative histological studies were used to establish the presence of a tumour and the completeness of removal. The final diagnosis of a prolactinoma was based on the results of histological studies, including specific immunoperoxidase staining, and of hormone assays on cell cultures.

Patients studied

Between October 1977 and September 1983, 77 women with a presumed prolactinoma underwent transsphenoidal exploration. In 69 patients a tumour was identified; of these, 61 were microprolactinomas (defined as being ≤10 mm in diameter) and eight were macroprolactinomas (>10 mm in diameter). Two patients had another lesion, and in six patients a tumour was not found.

Within a month after operation the basal serum prolactin concentration was estimated at least twice and anterior pituitary function and reserve were tested by standard methods. These tests, and the response of serum prolactin concentrations to thyrotrophin releasing hormone and metoclopramide, were repeated at varying intervals in individual cases. This report is based on the data available up to the period October to December 1984. Thus the minimum possible follow up period was one year and the maximum seven years (mean 3-6 years). Forty eight patients had been followed up for three or more years and 32 for five or more years.

Three patients moved away from Glasgow and so could not be followed up long term. Two had a normal serum prolactin concentration after operation, and in one the concentration remained normal for at least one year. The third patient had a raised serum prolactin concentration of 530 mU/l after operation.

Results

Table I shows the overall early and late results for the 77 patients. Normal prolactin concentrations were found in 53 patients after operation and persisted in 21 of the 23 patients with normal prolactin concentrations after operation followed up for more than five years.

Table II summarises the information about the patients with macroprolactinomas. They separated into two groups. Four patients had a preoperative serum prolactin concentration between 2000 and 5000 mU/l, in each of these the clinical problem was cured, and the serum prolactin concentration was restored to normal in three and almost to normal in one. In two of these patients the tumour was partly cystic, and this may explain the discrepancy between its size and the fairly low serum prolactin concentration. The remaining four patients had much more severe hyperprolactinaemia. Although in three the serum prolactin concentration was substantially lower after operation, in none did it reach normal. Remission of some of these patients’ symptoms occurred after treatment with bromocriptine.

Table I—Changes in serum prolactin concentrations after transsphenoidal operation in 77 patients with suspected prolactinomas

<table>
<thead>
<tr>
<th>Findings at operation</th>
<th>Range of preoperative serum prolactin (mU/l)</th>
<th>Early postoperative results</th>
<th>Results after five years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No of patients</td>
<td>% with prolactin &lt; 360 mU/l</td>
</tr>
<tr>
<td>Microprolactinoma</td>
<td>560-11 700</td>
<td>61</td>
<td>46 (73-4)</td>
</tr>
<tr>
<td>Macro adenoma</td>
<td>2000-83 000</td>
<td>8</td>
<td>4 (50-9)</td>
</tr>
<tr>
<td>Prolactinoma not found</td>
<td>1092-3880</td>
<td>8</td>
<td>3 (37-5)</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>77</td>
<td>53 (68-8)</td>
</tr>
</tbody>
</table>

Table II—Clinical problems in eight patients with macroprolactinomas before and after transsphenoidal operation

<table>
<thead>
<tr>
<th>Case No</th>
<th>Serum prolactin (mU/l)</th>
<th>Amenorrhea</th>
<th>Galactorrhoea</th>
<th>Infertility</th>
<th>Additional treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2 000</td>
<td>Cured</td>
<td>Cured</td>
<td>Cured</td>
<td>None</td>
</tr>
<tr>
<td>2</td>
<td>2 064</td>
<td>Cured</td>
<td>Cured</td>
<td>Cured</td>
<td>None</td>
</tr>
<tr>
<td>3</td>
<td>2 280</td>
<td>Cured</td>
<td>NA</td>
<td>None</td>
<td>Radiotherapy, bromocriptine</td>
</tr>
<tr>
<td>4</td>
<td>4 297</td>
<td>Cured</td>
<td>NA</td>
<td>None</td>
<td>Radiotherapy, bromocriptine</td>
</tr>
<tr>
<td>5</td>
<td>21 600</td>
<td>Not cured</td>
<td>NA</td>
<td>Cured†</td>
<td>Radiotherapy, bromocriptine</td>
</tr>
<tr>
<td>6</td>
<td>24 700</td>
<td>Not cured</td>
<td>Not cured</td>
<td>Cured†</td>
<td>Radiotherapy, bromocriptine, pergolide mesylate</td>
</tr>
<tr>
<td>7</td>
<td>73 790</td>
<td>Not cured</td>
<td>Not cured</td>
<td>Cured†</td>
<td>Radiotherapy, bromocriptine, pergolide mesylate</td>
</tr>
<tr>
<td>8</td>
<td>83 000</td>
<td>Not cured</td>
<td>NA</td>
<td>None</td>
<td>Radiotherapy, bromocriptine</td>
</tr>
</tbody>
</table>

NA = Not applicable.
*Patient had endometriosis; ovulation suggested by rise in progesterone concentrations.
†After treatment with bromocriptine.
Patients in whom a prolactinoma was not identified (n=8)

In one patient the pituitary contained tissue consistent with a diagnosis of sarcoidosis; another had a small chordoma that had eroded into the pituitary from the sphenoid bone. In both patients the serum prolactin concentration was in the normal range after operation and regular menstruation returned. Neither patient was seeking to become pregnant.

In the remaining six patients a tumour was not detected at operation and adenomatous tissue could not be found in the biopsy specimens taken. Two of these patients had a normal serum prolactin concentration after operation, recovered ovulatory menstrual function, and became pregnant. The remaining four patients still had hyperprolactinaemia; two became pregnant after treatment with bromocriptine, and two decided against attempting to conceive.

COMPLICATIONS AFTER OPERATION

Complications of the operation were usually minor bruising of the face and transient numbness of the upper lip. A brief nasal discharge was common, but in only 12 of the 69 patients with prolactinomas this was thought to be cerebrospinal rhinorrhoea. In each patient this resolved rapidly, and none required further operation. The only serious complication was a mild meningitic syndrome caused by Staphylococcus albino. The patient responded promptly to antibiotics, was cured of hyperprolactinaemia, and subsequently became pregnant.

Endocrine complications were likewise few. Transient diabetes insipidus was observed in seven patients, and 11 patients developed growth hormone deficiency. Only three patients received replacement treatment with cortisol after the immediate postoperative period, and two of these showed normal function of the hypothalamic pituitary adrenal axis when tested two and six years later; the other patient moved away from Glasgow and was not retested. Secondary hypothyroidism developed five years after operation in one patient.

RECURRENT HYPERPROLACTINAEMIA

Only three patients (4% of the total series) showed evidence of recurrent persisting hyperprolactinaemia. Each had a microprolactinoma, and recurrence occurred at three, 19, and 24 months after operation. These patients were discussed in a previous paper. One patient (patient 3 in table 2 of that paper) was later reviewed. She still had mild hyperprolactinaemia (420 mU/l) at three years but was menstruating and apparently ovulating. She had not become pregnant, and laparoscopy showed the presence of extensive endometriosis. Each of the three patients underwent high definition computerised tomography, which showed a small pituitary gland without evidence of an adenoma.

Four other patients had a transient rise in serum prolactin concentration; in three of these patients this subsequently reverted to normal without specific treatment. The fourth had late secondary hypothyroidism, and after treatment of this the hyperprolactinaemia resolved.

PATIENTS FOLLOWED UP FOR LONGER THAN FIVE YEARS

Thirty patients who had a prolactinoma (28 with microadenomas, two with macroadenomas) were followed up for more than five years after operation. Ten of these patients had hyperprolactinaemia at follow up. In eight this reflected the failure of the initial operation to reduce the serum prolactin concentration to entirely normal values. Of 22 patients with an initially successful operation, only two had recurrent hyperprolactinaemia.

Twenty one of the 30 patients wished to become pregnant; 17 were successful as a result of operation, and in two further patients pregnancy occurred after treatment with bromocriptine. Thus 19 of the 21 became pregnant.

Discussion

The successful early postoperative results in this series are comparable with those in other large series of patients treated by operation. The prospect that an effective operation also leads to a permanent cure has been one of the main arguments advanced for using operation as the primary treatment for a prolactinoma. In this series recurrence of hyperprolactinaemia was indeed rare after an initially successful operation. Our findings therefore contradict the
much greater certainty of final diagnosis in series of patients treated by operation. Fifth generation computed tomography might make it possible to establish confidently whether a patient has a microprolactinoma, but there is mounting evidence that many radiological "abnormalities" prove at operation to be unrelated to the presence of a tumour. Clearly, when only biochemical and radiological information is available a prolactinoma can often be only presumed to be present. There must be considerable doubt about what exactly is being treated when non-surgical methods are used.

We conclude that it is reasonable to offer a transsphenoidal operation to a woman with hyperprolactinaemia believed to be due to a prolactinoma. Surgery is clearly preferable to irradiation in patients who are thought to be of bromocriptamine or who do not wish to take drugs on a long term basis, but optimum results are obtained in patients with a small tumour and when operation is performed as the primary method of treatment. Although it is a highly specialised technique, the success of pituitary surgery for tumours producing growth hormone or adrenocorticotropic hormone has led to the skill needed to treat prolactinomas being available in several British centres.

We acknowledge our co-workers, E H McLaren, S Slater, J E Thomson, and C Thomson, who managed some of these patients and provided data for this report. We also thank Dr G Beattie (clinical biochemistry) for the hormone assays and our colleagues in neuroradiology and neuroradiology for their parts in the diagnosis and management of these patients.

References

MATERIA NON MEDICA

Footprints of crime

Exactly 300 years ago, in 1685, two brothers quarrelled over a "worthless woman" and fought a duel in Southampton Fields. The spot has since become familiar to visitors to BMA House under the name of Tavitsock Square. In the frenzy the brothers trampled the grass until one of them fell mortally wounded in an agonsed posture on the ground. The woman meanwhile watched them from a nearby bank. According to legend the depression made in the ground by the dead brother's body and their footmarks in the turf were visible as bare hollows a century later. A letter dated 1778 and published in the Gentleman's Magazine in 1804 recounts the story and tells how the traces remained on the ground despite attempts to obliterate them by ploughing. The writer of that letter had visited the spot and there saw, in addition to the duellists' traces, a hollow where the woman was supposed to have sat watching them.

This account of the legend comes from a delightful book by Jennifer Westwood, recently published, Albinon: a guide to legendary Britain (Granada, £12.95). As befits an author who is a graduate of both Oxford and Cambridge her text is scholarly and precise and she includes interesting comparative data. She notes for instance that the underlying theme of the legend was at one time commonly believed, namely the imprinting of the ground by the footsteps or bodies of people who had committed a crime there. Nor need the legend die yet. For she describes how she too visited the spot where the duel was fought—now the southwest corner of the lawn in Tavitsock Square —and tells us: "I am happy to report that there are bare patches there which could be taken for footprints." The curiosity to see these patches was also too much for me, so on a visit to BMA House a few weeks ago I visited the fatal ground. And I am delighted to say the patches are still there, irregular depressions partly bare of grass, where the brothers fought and one of them died under the gaze of the "worthless woman."—T D Y Swincoe, Devon.

Straightening up for the cup

I was always slightly landy, but a rugger accident in my student days, and the subsequent arthritis which developed, produced a remarkable increase in the bowing. When both my feet were touching each other you could almost smell the football between my knees. Friends could honestly cover me half a mile away by my legs, and some would inquire when I had been a jockey. Recently a knee replacement has produced a leg as straight as a ballet dancer's, but when walking I have a mild list to port and my wife hardly recognises me a hundred yards away.

The benefits of a knee replacement are not immediately apparent. Unlike after a hip operation recovery of full function takes several months and the patient must dedicate himself to a routine of ice packs, physiotherapy, and a good deal of patience. My surgeon tells me I shall probably be able to play golf this spring, but in the mean time I can only mow the lawn and the golf.