Incidentally found small pituitary adenomas may have no effect on fertility

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Abstract. Histological examination of the pituitary glands from 486 unselected autopsies revealed 97 clinically unsuspected adenomas in 78 glands (16%). Prolactinomas numbered 48; no hormone was found in 30, L.H in 8, ACTH in 7, growth hormone (GH) and prolactin in 3, and GH alone in 1. Eleven of 194 female subjects and 37 out of 292 males had one or more prolactinoma. Clinical case notes, available for 57 of 78 subjects with adenomas, were reviewed to obtain data on fertility. Of the 25 women with case notes, 6 of the 11 with prolactinomas and 11 of the 14 with adenomas of other types had conceived. For the 32 males, 10 of the 23 with prolactinomas and 5 of the 9 with other types had procreated. These findings show that pituitary tumours not identified in life may have no major anti-fertility effect, and suggest that treatment of small intrasellar lesions discovered clinically by chance may not be necessary.

The natural history of pituitary adenomas in man is complex. A proportion of such tumours are recognised clinically because of endocrine symptomatology or because of pressure effects on intracranial structures. A number of cases are discovered through the chance radiological finding of an abnormal sella turcica in patients without endocrine disease or clinical signs of an expansive lesion. However, all of these tumours are numerically overshadowed by the incidental pituitary tumours found at routine autopsy. In different series these have been shown to be present in between 8 and 30% of the population (Costello 1936; Burrow et al. 1981; McComb et al. 1983; Abd El-Hamid & Lewis 1985). They are found at all ages, though they tend to become more frequent with advancing age. About half are prolactinomas which show a different age distribution in the two sexes — peaking in middle life in women and in the seventh and eighth decade in men (personal data to be published). These tumours are generally less than 2 mm in diameter, but may reach a size (up to 6 mm in our material) at which they might be detectable radiologically. This fact, together with the observation (Rjosh et al. 1982) that the natural history of clinically recognised prolactinoma may be long and medically uneventful, suggests that incidental and overt tumours of this type may be a biological unity. In view of the effects on fertility of clinically diagnosed prolactinomas of middle life, it seemed of interest to evaluate retrospectively the fertility in cases where an incidental pituitary adenoma was discovered at autopsy. We have reviewed the reproductive history of patients of both sexes found to have prolactinomas in routine autopsies, as well as that of patients whose incidental adenomas contained other hormones.

Materials and Methods

A total of 486 pituitary glands from routine autopsies were examined, in horizontal section. Two randomly selected sections near the centre of each gland were investigated for the presence of adenomas, using standard histological methods and hormone immunocytochemistry with a peroxidase-antiperoxidase technique.
Clinical case notes, available in a proportion of cases, were reviewed and the total number of conceptions or children procreated (including abortions) was recorded. No information could be obtained concerning the incidence of loss of libido, complaints related to (PRL-mediated) low estrogen levels and/or osteoporosis in these patients.

Skull radiographs requested for non-endocrine reasons were available in 3 cases. These were evaluated for normality of pituitary fossa outline, and the length, depth and cross-sectional area of the fossae were measured and compared with normal ranges.

Results

1. Incidental adenomas

Seventy-eight pituitaries (16%) contained 97 adenomas ranging in diameter from 0.5 to 6.0 mm. The age of affected patients was 20 to 90 years. No sex preponderance was seen; 54 of the 292 male pituitaries (18%) contained adenomas, and 24 of 194 female glands (12%). Hormone immunostaining showed 48 of the 97 tumours (49.5%) to be prolactinomas, while 8 (8.2%) contained LH (1 also with TSH), 7 (7.2%) ACTH, 3 (3.1%) both GH and prolactin, and one GH only.

Thirty tumours (31%) were negative for the hormones studied (null tumours).

2. Female patients (Table 1)

In 25 female cases with adenomas, reproductive data were available. Of the 11 subjects with one or more prolactinomas, 6 (55%) had conceived, while of the 14 with other tumour types 11 (79%) had conceived. The age at death of women who had not conceived exceeded 39 in all members of both groups. The difference in numbers with conceptions in the two tumour groups was not significant ($\chi^2$ testing; $P < 0.2$). The total number of conceptions in the 6 fertile subjects with prolactinomas was 7, and in the 11 subjects with other tumour types 20. The overall fertility rate in females with incidental tumours was 68% (17/25).

3. Male patients (Table 2)

A total of 32 autopsies were performed on males with incidental adenomas for whom reproductive data were available. Of 23 who had one or more prolactinomas, 10 (45%) had produced offspring, while of 9 with other tumours, 5 (55%) had procreated. The total number of pregnancies produced by the 10 with prolactinomas was 12, and by the other 5 it was 11. Clearly neither incidental

<table>
<thead>
<tr>
<th>Hormone/s secreted</th>
<th>No. of tumours present</th>
<th>Total No. of subjects</th>
<th>No. of subjects who had conceived</th>
<th>Ages at death (range &amp; mean)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>One conception</td>
<td>Two or more conceptions</td>
</tr>
<tr>
<td>Women with prolactinomas</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PRL only</td>
<td>1</td>
<td>8</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>PRL &amp; PRL</td>
<td>2</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PRL &amp; null</td>
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<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>PRL &amp; null &amp; null</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>0</td>
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<tr>
<td>Total with PRL</td>
<td>3</td>
<td>11</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>Women with non-prolactin-containing tumours</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LH only</td>
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<tr>
<td>LH &amp; TSH</td>
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<td>0</td>
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<td>1</td>
</tr>
<tr>
<td>Null only</td>
<td>1</td>
<td>10</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Total without PRL</td>
<td>14</td>
<td>5</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>All tumours</td>
<td>25</td>
<td>10</td>
<td>7</td>
<td>17</td>
</tr>
</tbody>
</table>

Table 1.

Fertility in 25 women with pituitary tumours.
prolactinomas nor other pituitary adenomas have a major adverse effect on male fertility. The age at death for those cases where no pregnancies had been produced exceeded 28 years in all members of both groups.

4. Pituitary fossa radiographs

Case MT was a woman aged 46 at death with a central prolactinoma of 0.7 mm in diameter. The pituitary fossa films taken 3 days before death looked normal. Case GP was a woman aged 83 with a single null-hormone tumour of 2.1 mm in diameter situated in the right lateral wing. A double contour was seen in the lateral film taken 9 years before death and the floor sloped downward 1 mm to the right side of the A-P film. The dimensions were normal, but appearances were strongly suggestive of a tumour. Case LW was a male aged 51 who had a single prolactinoma of 1.8 mm in diameter situated in the central mucoid wedge. A double contour was seen in the lateral film, while in the A-P film there was a small dip in the midline. The dimensions were normal, but appearances were judged suspicious of abnormality.

Discussion

Over the last 50 years, it has been increasingly recognised that small pituitary adenomas are common in the general population, and can often be shown as incidental findings at autopsy in patients who had no clinical evidence of endocrine abnormality or sellar expansion. The frequency of such tumours varies from series to series, but probably about 15–20% of random autopsies reveal an incidental adenoma. The incidence of incidental pituitary tumours in this series (16%) lies in the middle of the published range. The inability to study serial sections of the pituitary gland in this study must to some degree underestimate the incidence and very small adenomas might be missed. The more recent reports (McComb et al. 1983; Abd El-Hamid & Lewis 1985) have shown with hormone immunocytochemistry that about half of these neoplasms are prolactin-containing, while most of the remainder are argyrophilic, and are either nonstaining for hormones or positive for LH and FSH (Abd El-Hamid & Lewis 1985).

Hitherto, the possibility of an effect of such
tumours on reproduction has not been assessed by a retrospective clinical study, though the question has doubtless often been raised. The present study goes some way to providing an answer. We recognise that the development of an incidental tumour may occur after the reproductive period. However, the incidental tumours that we found occurred at all ages, and in the case of females, prolactinomas were concentrated in the reproductive period. Long-term clinical and X-ray follow-up of untreated overt prolactinomas may show a striking lack of progression over many years (Cassar et al. 1984). We therefore consider that in many of our cases the tumour may have been present during the reproductive phase of life, in which case there appears to be no major adverse effect on male or female fertility. This finding has clinical relevance. Some incidental tumours, as we have shown, are large enough to produce skull radiological abnormalities, and may be evident on CT scan. Sellar X-ray abnormalities or small intrapituitary CT lesions are sometimes a chance finding in patients without endocrine abnormality. It would appear that invasive investigation and treatment of such lesions in an attempt to maintain fertility may not be necessary.

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References

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