Early post-operative growth hormone levels predict the result of transsphenoidal tumour removal in acromegaly

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Abstract. Serum human growth hormone (hGH) measurements were performed during transsphenoidal microsurgery for acromegaly and in the early period afterwards. There were 14 patients of which 2 were operated on twice. In 11 patients (2 patients at re-operation) the serum hGH concentration was normalized to less than 5 µg/l within 3 h after completion of surgery. On five occasions only partial restoration of the hGH values was obtained and additional treatment was given in 2 patients by successful re-operation. The early post-operative hGH concentrations were consistent with the clinical evaluation of the patients and the hGH concentrations during follow-up for an average of 27 months. We conclude that early post-operative serum hGH measurement is of value for evaluation of the efficiency of the tumour removal and the need for further treatment.

Acromegaly is a slowly progressing disease which, if untreated, results in a shortened life-length (Wright et al. 1970). By now, transsphenoidal microsurgery (Baskin et al. 1982) and conventional pituitary radiation (Eastman et al. 1979) appear to be the two therapeutic options considered as most effective and they also cause least damage (Christy 1982) to other hypophyseal functions. Both therapies may also be combined e.g. as initial microsurgery followed by radiation.

It is obvious that post-operative prognostic criteria are needed for identifying those who will deserve further therapy or at least closer control.

A dramatic fall in human growth hormone (hGH) concentration during operation and in the immediate hours after adenomectomy has been reported in acromegalic patients (Allen et al. 1974; Lüdecke et al. 1975, 1976; von Werder & Fahlbusch 1977).

The aim of the present study was to further evaluate peri-operative hGH measurements in predicting the efficiency of surgery for acromegaly. The results of peri-operative hGH concentrations were compared with those obtained during the follow-up in 14 acromegalic patients consecutively operated on by transsphenoidal microsurgery.

Material and Methods

Patients

Between 1978 and 1981 14 patients (7 females and 7 males) with previously untreated acromegaly were referred to our unit. The patient data shown in Table 1 include the grade of tumour extension based on neuro-radiological examinations and intra-operative findings (Hardy 1973; Baskin et al. 1982).

All patients had obvious clinical signs of active acromegaly and the diagnosis was confirmed by several analyses showing elevated basal hGH concentrations. The pituitary function was evaluated both pre- and post-operatively using both l.RH (100 µg iv) and TRH-stimulation (200 µg iv) tests and insulin-induced hypoglycaemia tests in all patients.

Surgical procedure

All patients were operated on by transsphenoidal microsurgery. The transseptal technique was used (Hardy...
Table I.
Clinical material.

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Sex</th>
<th>Age (years)</th>
<th>Tumour grade</th>
<th>Mean pre-operative hGH concentration (µg/l)</th>
<th>Pre-operative pituitary deficiency</th>
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<tbody>
<tr>
<td>1</td>
<td>M</td>
<td>32</td>
<td>III</td>
<td>134</td>
<td>Panhypopituitarism</td>
</tr>
<tr>
<td>2</td>
<td>M</td>
<td>44</td>
<td>III</td>
<td>209*</td>
<td>Gonadal, thyroid</td>
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<tr>
<td>3</td>
<td>F</td>
<td>54</td>
<td>I</td>
<td>76</td>
<td></td>
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<tr>
<td>4</td>
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<tr>
<td>5</td>
<td>F</td>
<td>41</td>
<td>II</td>
<td>168</td>
<td></td>
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<td>6</td>
<td>F</td>
<td>56</td>
<td>II</td>
<td>32</td>
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<td>F</td>
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<td>17</td>
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<tr>
<td>14</td>
<td>M</td>
<td>30</td>
<td>II</td>
<td>40</td>
<td></td>
</tr>
</tbody>
</table>

* Decreased to 15 µg/l after probably tumour necrosis 2 months before surgery.

1973). Two patients underwent a second operation. In patient 1 it was shown at the primary operation that the adenoma was invasively growing in the sellar dura. Supplementary dural excision was performed one year later via a second transsphenoidal approach. In patient 9 a suprasellar rest of the adenoma localized anterior to the sellar opening was not accessible from below. The remnant was removed by an intracranial subfrontal approach 4 months after the primary operation.

All operations were performed during a uniform procedure of neurolept anaesthesia. The patients were pre-medicated with atropin, diazepam, and droperidol, and at the same time, an infusion of 100 mg hydrocortisone iv was started. The anaesthesia was initiated by barbiturate and it was complemented with fentanyl, NO₂, droperidol, and pancuron.

Serum growth hormone studies
Samples of peripheral venous blood for serum hGH assays were obtained at fixed stages throughout the operative procedure, viz, at pre-medication, after intubation before the operative approach, during operation at the end of tumour removal and at 1 and 3 h after adenomectomy. The basal hGH level was also determined on the day after operation at 08.00 and 20.00 h.

In 2 patients (patients 13 and 14) an extended programme for serum sampling was performed during the operative procedure. Samples for hGH measurement were taken at pre-medication, immediately after intubation, before the sellar approach, during removal of the adenoma, at the end of adenomectomy and at 0.5, 1.5 and 3 h after the adenomectomy.

Growth hormone in serum was determined by a double antibody radioimmunoassay. hGH containing 2.0 IU/mg was obtained from AB Kabi (Stockholm) and this preparation was used as a standard.

Results
Transsphenoidal microsurgery resulted in only partial remission of the hGH values in 5 patients (Fig. 1). Two of them were re-operated and this resulted in a restoration of the serum hGH to normal concentrations (≤ 5.0 µg/l). Their results, obtained at re-operation, are therefore shown in Fig. 1 together with the main group of 9 patients whose hGH concentrations returned to less than 5.0 µg/l after surgery. In these 11 patients clinical improvements were achieved after surgery, and the low hGH concentrations were maintained (1.8 ± 1.2 µg/l, mean ± SD) during the follow-up period.

Extended intra-operative hGH determinations in 2 patients with remission (patient 13 and 14) are
Serum hGH levels during removal of pituitary tumours and in the early post-operative period in patients with acromegaly. Mean and SD of hGH concentrations are indicated for 11 patients with total remission (●—●) and 5 patients with partial remission (○—○). Samples of peripheral venous blood for hGH assays were obtained at pre-medication (P), after intubation (A), at the end of tumour removal (T), at 1 and 3 h after adenomectomy, and at 08.00 and 20.00 h the day after operation.

shown in Fig. 2. In both patients there were two peaks in hGH levels viz just after intubation and during adenomectomy.

One of the remaining 3 patients with partial remissions (patient 2), obtained a decrease of the hGH level to normal at 1 h after adenomectomy and this was maintained during the following year. Clinical, radiographic, and biochemical signs of tumour necrosis were present 2 months before surgery in this patient. The tumour tissue showed partial infarction and was growing invasively in the dura which was partly excised. Two years after surgery this patient received radiation therapy due to slight biochemical signs of tumour recurrence (hGH-concentrations about 10 µg/l).

Post-operatively radiation was given as a routine procedure to the first 5 patients with one exception as mentioned above (patient 2). Radiation therapy was later on restricted to patients with intra-operative findings of invasive tumours such as patient 9.

Complications to transsphenoidal surgery were few. One patient (patient 1) developed meningitis and a transient diabetes insipidus after the second transsphenoidal approach, but recovered completely after appropriate therapy. Another patient (patient 9), was treated by lumbar drainage due to CSF leakage during the immediate post-operative period. There were no additional post-operative endocrine deficiencies. Mean hGH-concentration during long-term follow-up (27 ± 18 months) for the 14 patients was 4.2 ± 5.8 (range 0.5—23) µg/l.

Discussion

Transsphenoidal microsurgery is an effective and safe treatment for acromegaly (Hardy 1973; Lüdecke et al. 1976; U et al. 1977; Laws et al. 1979; Balagura et al. 1981; Baskin et al. 1982). Several studies have shown that microsurgery can promptly cure the hGH hypersecretion in acromegaly (Allen et al. 1974; Lüdecke et al. 1975, 1976; von Werder & Fahlbusch 1977). This is in contrast to the very late response obtained by radiotherapy (Eastman et al. 1979).

The final surgical results in our patients are in agreement with those reported in previous series (Hardy 1973; Laws et al. 1979; Balagura et al. 1981; Baskin et al. 1982). A mean concentration of hGH less than 5 µg/l and clinical improvement were obtained in 11 out of 14 patients (79%). There was a partial remission of the disease in the remaining 3 patients and, moreover, surgical treatment did not result in any pituitary deficiencies. A longer follow-up, however, is necessary to determine the final outcome of the surgical treatment. One patient presented biochemical evidence of tumour recurrence after achieving normal hGH concentrations both immediately after surgery and during the first post-operative year. We suppose that the established in invasive growth of tumour in the dura was the cause of recurrence in this case.

All patients with successful surgery achieved normal hGH levels within 3 h after adenomectomy which tallies with previous results by Lüdecke et al. (1976). The hGH concentration did not drop to normal in patients who were not restored at the evaluation 1 to 3 months after surgery. Thus,
peri-operative and early post-operative hGH levels were useful as an index to predict the result of tumour removal in spite of the complex situation that anaesthesia and surgery may constitute. The extended peri-operative hGH study showed that a peak level was achieved during the operative manipulation of the tumour. This level will determine the time it takes to reach reliable stable hGH concentrations. With a half-life disappearance of serum hGH of about 14 min (Lüdecke et al. 1975) it will be possible to study the immediate response to surgery during basal conditions in most patients i.e. when they still are under anaesthesia. A time-lag of less than 90 min is required to reach normal hGH concentrations after a peak value of less than about 150 µg/l. In patients with hGH concentrations of more than 150 µg/l during the removal of the tumour there is a risk that extubation and post-operative illness will influence the reliable stable hGH level.

Peri-operative and early post-operative hGH analysis for verifying the efficacy of tumour removal will spare much time and trouble for the patients. Probably these early values are more reliable than later values obtained during the first post-operative days when various other stress factors may influence GH-secretion. A minority of patients may need additional treatment with radiotherapy, drugs or a re-operation. The best supplemental treatment for those patients whose peri-operative hGH analyses are not normalized is probably, chosen at the time when clinical, endocrinological, radiographic, surgical, and histological findings are still fresh. It may also be of great importance for the surgeon to gain an early impression of the success of the surgical procedure.
Acknowledgments

We wish to thank Mrs. Gun Johansson for skilful secretarial assistance.

References


Received on September 10th, 1982.