Interrelationships between tumour size, age, plasma growth hormone and incidence of extrasellar extension in acromegalic patients

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Abstract. In 44 consecutive acromegalic patients we studied the interrelationships between tumour size, age, incidence of extrasellar extension, growth hormone levels and 'tumour growth'. These parameters were compared with results from a previous study in 62 prolactinoma patients. It appeared that the incidence of extrasellar extension in acromegalic patients was lower than in the prolactinoma patients (32 versus 44%). In acromegalic patients extrasellar extension occurred on the average at a lateral sellar and tumour area of almost 1 cm² larger than in prolactinoma patients (with respect to sellar size generally above 3 cm² versus 2 cm², with respect to tumour size generally above 4 cm² versus 3 cm²).

Log tumour size and log basal growth hormone level were positively correlated (P < 0.0005). In the acromegalic patients there was a negative correlation between the size of the pituitary tumour and the age of the patient (P < 0.005) in contrast to the absence of such a relationship in the prolactinoma patients. In the group of acromegalic patients mean tumour size decreased gradually from the third to the sixth decade (5.0, 3.8, 3.0 and 2.3 cm², respectively). The interval between the time of appearance of symptoms and the time of diagnosis was significantly shorter in younger patients and in women. The restriction of large tumours (lateral area > 5 cm²) to young patients (< 35 year) and the short period between the appearance of symptoms and the time of diagnosis in these patients indicate that growth hormone secreting pituitary tumours generally grow more rapidly in younger patients.

In patients with a pituitary tumour extrasellar extension of the tumour constitutes one of the major complications. In a previous study we demonstrated that in 62 patients with hyperprolactinaemia and a pituitary tumour a sellar size or a 'tumour size' of 2–3 cm² – as measured directly with a planimeter on the lateral X-ray of the skull – represented a critical limit for the presence of extrasellar extension of the pituitary adenoma (Klijn et al. 1980b). A positive correlation between tumour size and the plasma prolactin (Prl) level was found. In acromegalic patients such a correlation between tumour size and basal growth hormone (GH) level is not well established up to now (Quabbe 1980; Giovanelli et al. 1980). Pituitary tumours occur at all ages from puberty onwards, but little is known about the influence of age on tumour size and growth.

The aim of the present study was to answer the following questions. 1) Is the incidence of extrasellar extension in acromegalic patients different from that in patients with Prl secreting tumours? 2) Are tumour size and basal plasma GH concentration related? 3) What is the influence of the age of the individual on tumour growth rate in acromegaly and on the chance of extrasellar extension?

Part of these data have been presented at the 2nd European Workshop on Pituitary Adenomas (Paris, September 1979).

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Materials and Methods

Patients
Forty-four consecutive acromegalic patients (21 women and 23 men) were investigated. They were referred to our endocrine clinic by specialists in internal medicine (n = 16), gynaecology (n = 5), neurology or neurosurgery (n = 6), ophthalmology (n = 2), rheumatology or orthopaedy (n = 6), urology (n = 3) or – incidentally – other specialists. All patients were untreated at the time of study. In 32 of them the presence of a pituitary tumour was proven by surgery. The others were not operated upon. The results of this study were compared with those of a previous investigation of 62 patients (38 women and 24 men) with hyperprolactinaemia and a pituitary tumour without growth hormone excess (Klijn et al. 1980b and in press).

Table 1.
Referred pattern and clinical features in 44 consecutive acromegalic patients.

<table>
<thead>
<tr>
<th>Mode of presentation</th>
<th>Overall prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
</tr>
<tr>
<td>Change of appearance/soft tissue swelling/acral growth</td>
<td>6</td>
</tr>
<tr>
<td>Weight gain</td>
<td>–</td>
</tr>
<tr>
<td>Gigantism</td>
<td>–</td>
</tr>
<tr>
<td>Acroparaesthesias</td>
<td>3</td>
</tr>
<tr>
<td>Facial neuralgias</td>
<td>–</td>
</tr>
<tr>
<td>Arthropathy</td>
<td>2</td>
</tr>
<tr>
<td>Back pain</td>
<td>1</td>
</tr>
<tr>
<td>Tiredness</td>
<td>1</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>1</td>
</tr>
<tr>
<td>Thirst (without diabetes insipidus)</td>
<td>1</td>
</tr>
<tr>
<td>Hypertrichosis</td>
<td>–</td>
</tr>
<tr>
<td>Ear/nose/throat complications</td>
<td>1</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4</td>
</tr>
<tr>
<td>Cardiac complications</td>
<td>2</td>
</tr>
<tr>
<td>Impaired glucose tolerance</td>
<td>–</td>
</tr>
<tr>
<td>Manifest diabetes mellitus</td>
<td>–</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>3</td>
</tr>
<tr>
<td>Inguinal or umbilical hernia</td>
<td>–</td>
</tr>
<tr>
<td>Renal stones</td>
<td>3</td>
</tr>
<tr>
<td>Goitre</td>
<td>18*</td>
</tr>
<tr>
<td>Headache</td>
<td>6</td>
</tr>
<tr>
<td>Hypersomnolence</td>
<td>–</td>
</tr>
<tr>
<td>Loss of concentration and/or memory</td>
<td>–</td>
</tr>
<tr>
<td>Visual impairment</td>
<td>2</td>
</tr>
<tr>
<td>CSF-rhinorrhoea</td>
<td>–</td>
</tr>
<tr>
<td>Oligo-, amenorrhoea/infertility</td>
<td>5</td>
</tr>
<tr>
<td>Impotence</td>
<td>1</td>
</tr>
<tr>
<td>Loss of libido</td>
<td>–</td>
</tr>
<tr>
<td>Galactorrhoea</td>
<td>1</td>
</tr>
<tr>
<td>Cystic mastopathy</td>
<td>–</td>
</tr>
<tr>
<td>Diagnosis by chance</td>
<td>2</td>
</tr>
</tbody>
</table>

* One patient with a papillary carcinoma.
** Percentage of the female patients.
*** Percentage of the male patients.
Methods and materials

All patients were investigated by plain radiography, lateral polytomography (hypocycloidal, sections of 2 mm) and complete ophthalmological evaluation, including perimetry. Further radiological examination consisted of air-encephalography (AEG) and – in most cases – carotid angiography. As a measure of tumour size we have chosen the largest lateral area of the sella in combination with that of extrasellar tissue (EST), if present. The largest lateral area of the sella + EST was measured on a plain lateral X-ray after verification of the true sellar and extrasellar tissue outlines by means of lateral polytomography and the lateral tomograms of the AEG. Direct surface measurements were carried out with a planimeter as described in detail before (Klijn et al. 1980b). Normal values for sellar size are between 0.7 and 1.4 cm² (95% range in 100 patients without pituitary pathology). The area of the sella (+ EST) was also measured by means of square mm paper.

Plasma GH levels were measured by a homologous radioimmunoassay (IRE, Belgium), and Prl according to Kwa et al. (1973). Normal basal Prl values are up to 15 and 12 ng/ml for women and men, respectively. The biochemical diagnosis of acromegaly was made on the basis of a suppression of plasma GH concentrations to less than 5 ng/ml in response to an oral glucose load (100 g).

Statistical analysis of the data was performed using regression analysis, two-tailed Student’s t-test or X²-test.

Results

Epidemiological and clinical evaluation

The mean age of the 21 female patients was 39 years (median 40 years, range 19—74 years) and of the male patients 40 years (median 41 years, range 21—71 years). There was a preponderance of patients between 20 and 50 years. Histological examination of tumour material of the 32 operated patients revealed the presence of a chromophobe adenoma in ten cases, an acidophil adenoma in nine cases and a mixed adenoma in nine cases. In four patients a precise histological diagnosis was not obtainable.

The referral pattern and clinical features are summarized in Table 1. One of the acromegalic women menstruated regularly, nine were (post) menopausal and 11 had secondary oligo- or amenorrhoea. The mean duration of the secondary menstrual disorder was 4.5 years (range ½—15 years). Amenorrhoea occurred in three patients after cessation of oral contraceptive treatment and in one patient after childbirth. In 10 of these 11 patients with oligo- or amenorrhoea the plasma Prl level was estimated. Three of them had a high basal Prl level (137, 174 and 183 ng/ml, respectively), six a mild hyperprolactinaemia (range 19—43 ng/ml)

![Fig. 1.](attachment:image)

Tumour size (= lateral area of the sella + extrasellar tissue) in relation to the presence of extrasellar extension by radiological and perimetric criteria in 44 untreated acromegalic patients. There is some overlap of the groups of patients represented in the upper three panels (B, C, D). A patient may be represented in one, two or three of these panels. Closed symbols represent female, open symbols male patients.
and one a normal Prl level (4 ng/ml). Galactorhoea occurred in 10 out of 44 patients, all women (mean age 30 years, none of them older than 50 years). All but one had hyperprolactinaemia.

**Radiological and ophthalmological evolution**

In all patients the sella turcica was enlarged. The lateral area of the sella + EST varied between 1.5 and 13.6 cm² with a mean of 3.64 cm². There was no difference in tumour size between women and men (3.50 ± 1.69 cm² versus 3.76 ± 2.63 cm²; mean ± SD). In 14 patients (32%) extrasellar extension of the tumour was present radiologically (mean sellar + EST size: 5.9 cm²). Ten patients (23%) have suprasellar extension, six (14%) of them with visual field defects and one of them with infrasellar extension. Four patients showed infrasellar extension of the tumour only (Fig. 1). In the 30 patients without extrasellar extension mean sellar size was 2.6 cm². Extrasellar extension occurred only at tumour sizes of more than 3 cm², namely in 14 out of 22 patients with a tumour size of more than 3 cm² (64%). However, only two out of nine patients with a tumour size between 3 and 4 cm² showed extrasellar extension, while at a tumour size of above 4 cm² extrasellar extension was present in 12 out of 13 patients (92%). Besides the increase in size the sella turcica of 37 patients was more or less asymmetrical. In 20 cases the left side was larger, in 17 cases the right side.

When we take into consideration the size of the sella only (i.e. without the area of EST, if present) two patients with a tumour size of more than 3 cm² turned out to combine extrasellar extension with a sellar size of less than 3 cm² (2.5 and 2.4 cm²). This means that of the 23 patients with a sellar size of less than 3 cm² only two had evidence of extrasellar extension (9%) in contrast of 12 out of 21 patients with a sellar size exceeding 3 cm² (57%). Taking the group of patients with a sellar size between 2 and 3 cm² only two out of 16 patients had extrasellar extension (13%).

![Graph](image)

**Fig. 2.**

Correlation between log tumour size (= lateral area of the sella + extrasellar tissue) and log basal growth hormone in 44 untreated acromegalic patients (r = 0.59; P < 0.0005). Closed symbols represent female patients.
There was good agreement between the results of the two different methods of area measurements of tumour (n = 44; r = +0.993; P < 0.0005). The slope of the regression line was 1.004, the intercept -0.14 cm².

**Endocrinological evaluation**

Growth hormone was measured in all 44 patients before treatment. The basal GH level (mean of 2 or more estimations) varied between 7 and 720 ng/ml with a mean of 81 ng/ml in the female patients and 59 ng/ml in the male patients. There was a positive correlation between the logarithm of the sellar + EST area and the logarithm of the (average) basal GH level (Fig. 2). Furthermore a positive correlation was found between log tumour volume (½ x H x D x W according to Di Chiro & Nelson 1962) and log basal GH in those patients in whom the

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**Fig. 3.**

Correlation between age and tumour size (= lateral area of the sella + extrasellar tissue) in 44 untreated acromegalic patients (r = 0.48; P < 0.005). In panel A the arrows represent SEM. Closed symbols indicate female patients.
width of the sella floor was measurable on an anteroposterior plain X-ray (n = 36, r = 0.48; P < 0.01). A good correlation appeared to exist between the area and volume measurements of the tumours (n = 36, r = 0.955, P < 0.0005) as previously also found in patients with hyperprolactinaemia and a pituitary tumour (Klijn et al. 1980b).

Hyperprolactinaemia was observed in 13 (54%) out of 24 untreated patients. Prolactin levels of more than 100 ng/ml were found in only three of these patients.

Data with regard to pituitary-target organ function in these patients before treatment have been published before (Klijn et al., in press). Hypothyroidism was encountered in only one patient. This is to be compared to the occurrence of a low TT4 level (<6 µg/100 ml) in 31% of prolactinoma patients with the same range of tumour size as found in the acromegalic patients (≥1.5 cm²). An abnormal metyrapone test was found in four out of the 36 investigated acromegalic patients (11%; tumour sizes: 2.7, 4.1, 6.9 and 7.0 cm²). In the group of prolactinoma patients with an enlarged sellar area (≥1.5 cm²) an impaired metyrapone test was found in eight out of 33 patients (24%). A decreased gonadotrophin secretion was present in 12 out of 42 (29%) investigated acromegalic patients (in contrast to about 50% of the prolactinoma patients with the same range of tumour size). All these 12 patients had tumour sizes of more than 2.5 cm² (only two of them below 3 cm²).

Relation of age to tumour size and tumour growth rate
In the acromegalic patients we found an evident negative relationship between tumour size and age (Fig. 3A and B). The mean tumour size decreased
Table 2.
Mean delay (in years) between start of symptoms and time of diagnosis.

<table>
<thead>
<tr>
<th>Age group (years)</th>
<th>Women</th>
<th>n</th>
<th>Men</th>
<th>n</th>
<th>Total</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>19–30</td>
<td>2.1</td>
<td>8</td>
<td>4.2</td>
<td>5</td>
<td>2.9</td>
<td>13</td>
</tr>
<tr>
<td>31–40</td>
<td>5.0</td>
<td>3</td>
<td>9.3</td>
<td>7</td>
<td>8.0</td>
<td>10</td>
</tr>
<tr>
<td>41–50</td>
<td>7.2</td>
<td>5</td>
<td>10.1</td>
<td>6</td>
<td>8.8</td>
<td>11</td>
</tr>
<tr>
<td>51–70</td>
<td>3.6</td>
<td>5</td>
<td>10.4</td>
<td>5</td>
<td>7.0</td>
<td>10</td>
</tr>
<tr>
<td>All patients</td>
<td>4.1±3.1* years</td>
<td>21</td>
<td>8.6±5.1* years</td>
<td>23</td>
<td>6.5 years</td>
<td>44</td>
</tr>
</tbody>
</table>

* P < 0.001

gradually from the third to the sixth decade (4.98 ± 3.04; 3.82 ± 1.89; 3.02 ± 0.92; 2.30 ± 0.75; mean ± sp). This contrasts with the findings in our group of prolactinoma patients (Fig. 4). The nine acromegalic patients with the largest tumours (> 5 cm²) were all younger than 35 years. Likewise 10 out of the 14 patients with extrasellar extension were less than 35 years old. On the other hand 15 out of 18 patients with a tumour size below 2.5 cm² were more than 35 years old. All three histological tumour types (acidophil, chromophobe, or mixed) were present in the group of patients with large tumours.

As to the mean period between the time of onset of symptoms of acromegaly and the time of diagnosis, two points are remarkable (Table 2). Firstly this delay was found to be shorter in younger patients and secondly there was a significant difference between women and men of all ages (4.1 year and 8.6 year, respectively, P < 0.001.).

Discussion

The frequency of the various clinical manifestations of acromegaly in our patients is on the whole in reasonable agreement with previous reports (Davidoff 1926; Davis 1941; Kellgren et al. 1952; Wright et al. 1970; Hirsch et al. 1969; Daughaday 1974). The high frequency of tiredness without hormonal insufficiency might be explained by myopathy (Mastaglia et al. 1970), abnormal joint mechanics (Kellgren et al. 1952), peripheral neuropathy caused by soft tissue swelling and perineural or endoneural fibrous proliferation (Daughaday 1974) and/or cardiac disease (Hirsch et al. 1969). Remarkable was a relatively high frequency of inguinal hernia in our acromegalic men (30%).

The incidence of extrasellar extension in the acromegalic patients (32%) was lower than in the prolactinoma patients (44%), whose data we reported before (Klijn et al. 1980b). With respect to pituitary tumour size extrasellar extension is uncommon below a size of 3 cm² in both groups of patients. However, above a tumour size of 5 cm² the frequency of extrasellar extension is lower in the acromegalic (64%) than in the prolactinoma patients (92%), as there appears to be a cluster of acromegalis with a tumour size of between 3 and 4 cm² without extrasellar extension (Fig. 1). However, at tumour sizes of more than 4 cm² extrasellar extension occurred in 92% of the acromegalic patients also.

Using the lateral sellar area (i.e. without the area of EST) a lower incidence of extrasellar extension of the tumour was again observed in acromegaly as compared to prolactinoma patients. In the patients with a sellar size of less than 3 cm² radiological evidence of extrasellar extension was found more frequently in the prolactinoma patients than in the acromegalis (17% versus 9%), as especially reflected in the relatively high incidence of extrasellar extension in prolactinoma patients with a sellar size between 2 and 3 cm² (33% versus 13%). In the patients with a sellar size of more than 3 cm² the frequency of extrasellar extension was also higher in the prolactinoma patients than in the acromegalis (90% versus 57%). In summary it appeared that on the average in acromegalic patients extrasellar extension occurred at sellar and tumour sizes of 1 cm² larger than in prolactinoma patients (for tumour size 4 cm² versus 3 cm², for sellar size 3 cm² versus 2 cm²). In our experience ballooning of the pituitary fossa occurred frequently in acromegaly as also reported by Pribram & du Boulay (1971). We think that the lower frequency of extrasellar
extension and the occurrence of this complication at larger tumour sizes in acromegalic patients may be caused by a (indirect) GH effect on the sella turcica wall itself. Growth hormone was found to be the most effective bone growth stimulating pituitary hormone’ (Thorngren & Hansson 1977). We propose the following hypothesis. Acromegalic patients have an increased bone tissue turnover rate with increased periostial bone formation (Roelfsema 1972; Daughaday 1974). The pituitary fossa bone wall may therefore adapt more easily to the pressure of an expansive pituitary tumour than when a pituitary tumour is present without GH excess. It is also possible that in acromegalic patients the pituitary fossa tends to increase in size anyhow just as the frontal, mastoid and ethmoid sinuses may enlarge considerably. However, with further increasing tumour size the intrasellar pressure will ultimately be sufficiently high to cause extrasellar extension, but at larger tumour sizes in acromegalic patients than in patients with other pituitary tumour types.

Hypothyroidism, decreased gonadotrophin secretion and insufficient pituitary adrenal function occurred also less frequently in the acromegalic patients than in our group of patients with hyperprolactinaemia and a pituitary tumour, especially when the same range of tumour size is considered (i.e. after exclusion of the microprolactinomas). In acromegalic patients, however, a high incidence of an impaired TSH response to TRH has been noted (Hall et al. 1972; Klijn et al., in press) and a discrepancy between LH and FSH secretion (Lindholm et al. 1977). This might be explained by an effect of GH on thyroid, gonads and adrenals (for example development of goitre with suppression of TSH secretion) or on hypothalamic function.

We found a positive correlation between tumour size and basal plasma GH level, as we reported before for tumour size and the basal plasma Prl level in patients with a prolactinoma (Klijn et al. 1980a,b). In the group of acromegalic patients with a small adenoma (< 3 cm²) such a relationship was not present. This is in agreement with the findings of Giovanelli et al. (1980), who found no significant correlation between plasma GH concentration and tumour size in 57 acromegalic patients with small intrahypophyseal GH-secreting tumours (less than 13 mm in diameter at operation). It is noteworthy that in our group of patients there may be a wide range of plasma GH levels for a certain tumour size. Quabbe (1980) found also that small tumours may be accompanied by relatively high plasma GH concentrations, while larger tumours may have relatively low secretory activity. However, our data indicate that plasma GH levels of more than 50 ng/ml are associated predominantly with a tumour size of more than 2.5 cm².

Pituitary tumours may become manifest at an early age or later in life. The declining incidence of microprolactinomas in older patients (Fig. 4) may be explained by a lack of symptomatology. The true incidence may however be inferred from the frequency of microadenomas in routine autopsies, reported as 2.7% (Hardy 1978), 9% (McCormick & Halmi 1971), and 22.5% (Costello 1935), the frequency of microprolactinomas 6% (Kovacs et al. 1979) and the observation of Kovacs et al. (1979) that 8% of a group of geriatric patients had an elevated plasma Prl level.

We know of no previous data concerning a negative correlation between pituitary tumour size and age. In our series of patients with acromegaly large tumours above 5 cm² appeared to be uncommon in older patients but were frequent (about 50%) in patients younger than 35 years. A second interesting finding is the relatively short period intervening between the onset of symptoms of acromegaly and the time of diagnosis in the younger patients. These two observations indicate that on the whole GH-secreting pituitary tumours grow more rapidly in the younger than in the older patients. Gonadal steroids might be implicated in this respect. The longer delay between the clinical appearance of acromegaly and the time of diagnosis found in men as compared to women might be explained by the fact that men are not so rapidly alarmed by changes in their appearance than women. On the other hand photographs taken over the years often show that hypersonomatotropism must have been present years before complaints are noted. Therefore, some of the GH secreting pituitary tumours, arisen in younger patients, grow rapidly and others grow more slowly as tumours do in older people. On the basis of our findings treatment of acromegaly should be more aggressive in younger than in older patients.

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