Development of acromegaly in patients with prolactinomas

Marianne Andersen, Casper Hagen, Jan Frystyk, Henrik Daa Schroeder and Claus Hagen

Department of Endocrinology, Odense University Hospital, 5000 Odense C, Denmark, 1Medical Research Laboratory, Institute of Experimental and Clinical Research, University Hospital of Aarhus, DK-8000 Aarhus, Denmark and 2 Department of Pathology, Odense University Hospital, Denmark

(Correspondence should be addressed to Marianne Andersen; Email: M.Andersen@dahlmed.dk)

Abstract

Objectives: Patients with prolactinomas and patients with acromegaly often have heterogenous adenomas. In this study we have focused on patients with prolactinomas who developed acromegaly and acromegalic patients with hyperprolactinaemia. Our hypothesis is that some patients with hyperprolactinaemia may develop clinical acromegaly.

Methods: We have included patients examined at department M, Odense University Hospital between 1996 and 2001. Seventy-eight patients with prolactinomas, 65 females and 13 males, with a median age (range) of 30 years (14 – 74) and 47 years (20 – 66), respectively, were included in the study.

Results: In females and males the median prolactin (PRL) levels were 90 mg/l (27 – 4700; normal values (NV) < 23) and 1075 mg/l (24 – 6500; NV < 14), respectively. The PRL levels were significantly higher in males compared with females (P < 0.002). Fifty-nine patients with acromegaly, 24 females and 35 males, with a median age (range) of 45 years (24 – 70) and 53 years (19 – 70), respectively, were included. Seven of the 24 females had hyperprolactinaemia, with PRL levels of 90 mg/l (27 – 494). Thirteen of the 35 males had hyperprolactinaemia with PRL levels of 47 mg/l (17 – 251).

Three females with prolactinomas developed acromegaly clinically and biochemically. These patients had a normal low GH level and/or a normal IGF-I level at first diagnosis.

Conclusions: Our findings suggest that there is a common group of patients with a pituitary adenoma who secrete PRL and GH unsynchronously. Some of these patients have clinical acromegaly at diagnosis and some patients diagnosed as prolactinomas will develop acromegaly. We suggest an annual IGF-I measurement as a screening test.

European Journal of Endocrinology 149 17–22

Introduction

It is well known that hyperprolactinaemia is found in about 30–40% of acromegalic patients (1). In some acromegalic patients or patients with elevated prolactin (PRL) levels without acromegaly, the increased PRL levels may be a result of anatomical or functional hypothalamic–pituitary disconnection, but the existence of mixed growth hormone (GH)/PRL adenomas has been demonstrated (2). In human fetal (3) and adult (4) pituitaries it has been reported that GH and PRL can be stored and secreted by the same normal pituitary cells. These mammosomatotroph cells account for 25–50% of all cells in human pituitaries (4). It has been suggested that mammosomatotroph cells comprise a significant portion of the cell population in pituitary adenomas from acromegalic patients (3–6). We have previously reported that octreotide treatment for 4 weeks normalised PRL levels in patients with acromegaly and hyperprolactinaemia (7). In accordance with these results treatment with dopamine-D2 agonists suppressed GH secretion more efficiently in acromegalic patients with hyperprolactinaemia compared with those with normoprolactinaemia (8). Determination of serum insulin-like growth factor (IGF)-I levels may prove to be useful as a screening tool for adenomatous GH secretion in patients with prolactinomas (9). Circulating IGF-I has a half-life of several hours and originates in the liver; although it is produced in other tissues as well (10). GH is the major determinant of circulating IGF-I levels and it is through IGF-I that most, though not all, GH-mediated actions occur (9).

The consensus on the diagnosis of acromegaly was published recently (11). However, the development of acromegaly clinically and biochemically is probably a continuum from normal biochemistry to the full clinical picture (12). We wanted to test the hypothesis that hypersecretion of PRL and GH may develop and appear unsynchronously and therefore some patients with hyperprolactinaemia may develop acromegaly. In this study we have studied patients with prolactinomas.
and we have included patients with acromegaly for comparison of age, sex and PRL levels.

Materials and methods

Prolactinoma

During the last 5 years we have routinely screened for GH hypersecretion in most patients with prolactinomas using determinations of serum IGF-I levels. We have included all patients examined at department M, Odense University Hospital between 1996 and 2001. Seventy-eight patients with prolactinomas, 65 females and 13 males, with a median age (min-max) of 30 years (14–74) and 47 years (20–66), respectively were included in the study. No patient had clinical symptoms of GH-, adrenocorticotrophin (ACTH)- or thyrotrophin (TSH)-hypersecretion - all patients had normal TSH levels. No patient had symptoms or biochemical evidence of other causes of hyperprolactinaemia. No patient was taking any medication known to stimulate PRL. In 51/78 patients we had serum IGF-I measurements at diagnosis. In a further seven patients we had GH measurements. Magnetic resonance (MR) scans were carried out in 52 patients and computed tomography (CT) scans were used in 26 patients. At diagnosis 19 out of 65 females had macroadenomas (>10 mm), and 37 patients had microadenomas. An adenoma could not be visualized in nine patients (six MR scans and three CT scans). Ten out of 13 males had macroadenomas, three patients had microadenomas. In patients that developed elevated IGF-I levels, an oral glucose tolerance test (OGTT) was performed. In one patient (number 7) a random GH level was 0.29 mU/l and no OGTT was performed. Eight out of 65 females were treated with oestradiol and 45 patients were treated with a dopamine-D2 agonist. Pituitary surgery was performed in three patients (Table 1), one of these patients had surgery before the development of acromegaly (patient no. 2).

Paraffin sections, 4 m thick, were stained with the Invision technique for visualisation of human (h) GH and PRL (primary antibodies: polyclonal anti-hGH (DAKO, Copenhagen, Denmark) and monoclonal anti-PRL (NCL-Pro, Novocastra, Newcastle, UK)). Double staining was performed as combined Invision and two layer alkaline phosphatase detection techniques (DAKO).

Acromegaly

Fifty-nine patients with acromegaly, 24 females and 35 males, with a median age (min-max) of 46 years (24–70) and 53 years (19–70) respectively were included. The mean age for all patients was 47 years. All patients had active acromegaly in accordance with the consensus report (11). At diagnosis, 12 out of 24 females and 20 out of 35 males had macroadenomas. An adenoma could not be visualised by MR scans in three patients (two males and one female). MR scans were carried out in 26 patients and CT scans were used in 33 patients. IGF-I levels were measured in 48 out of 59 patients at first diagnosis.

Biochemical analysis

Prolactin was determined using an immunofluorometric assay (Delfia, Wallac Oy, Turku, Finland). The intra-assay coefficients of variation for PRL were 2.4% at 7 μg/l and 2.5% at 20 μg/l. The maximal range values for females and males are 23 μg/l and 14 μg/l, respectively.

Serum IGF-I was measured after extraction with HCl/ethanol (30 μl serum in 750 μl). After centrifugation the supernatant was further diluted 1:40 in assay buffer. IGF-I was then determined using an immunofluorometric sandwich assay with two monoclonal antibodies following the Delfia principle and using an AutoDelfia reader (Wallac Oy). The sensitivity limit was 2.5 ng/l. Intra- and interassay coefficients of variation were lower than 1.9% and 8.6% respectively. The 97.5 percentiles, +2 s.d., and (the 95% confidence intervals (CI) for the percentiles) for IGF-I according to age were: < 29 years 382 μg/l (418 μg/l); 30–39 years 257 μg/l (273 μg/l); 40–49 years 239 μg/l (256 μg/l); 50–59 years 202 μg/l (220 μg/l); and ≥60 years 201 μg/l (219 μg/l).

GH levels were determined by an immunofluorometric assay (Delfia, Wallac Oy). The level of detection for the Delfia assay was 0.03 mU/l. The intra-assay

| Table 1 Parameters for the three patients who developed acromegaly. |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Patient no.   | Sex | Age (years) | Follow up (months)* | PRL (μg/l) | IGF-I (μg/l) | GH (mU/l) | PRL (μg/l) | IGF-I (μg/l) | GH (mU/l) | Micro or macro | Immunohistochemistry |
| 1              | F   | 35          | 60               | 400         | 271         | 0.6     | 45            | 803           | 32 G         | Macro        | GH                     |
| 2              | F   | 49          | 29               | 790         | 162         | 5       | 328*          | 819           | 4.8 G        | Macro        | PRL§                  |
| 3              | F   | 39          | 40               | 196         | 270         | ND      | 44*           | 383           | 18 G         | Micro        | PRL, GH               |

*pTime until second diagnosis; +dopamine-D2-agonist therapy; G, nadir GH levels during an OGTT; ND, not done; §the operation was after the first diagnosis. No surgery the 2nd time. Significantly elevated IGF-I values are written in bold.
coefficients of variation for GH were 7% at 0.5 mU/l and 3% at 18 mU/l.

**Statistical analyses**

Data are presented for each individual and as the median (range) or mean ± S.E.M.; P values less than 5% were considered statistically significant. The Wilcoxon signed rank test was used for testing paired differences, and the Mann–Whitney U test was used for comparing differences between two groups. IGF-I levels above the 95% CI for the 97.5 percentile were considered significantly increased. The 'last visit' was the visit where an increased IGF-I was recorded for the first time.

**Results**

**Prolactinoma**

The median (range) PRL levels in all patients were 100 µg/l (24–6500). In females and males the median PRL levels were 90 µg/l (27–4700) and 1075 µg/l (24–6500), respectively. The PRL levels were significantly higher in males compared with females (P < 0.002). Three females developed acromegaly clinically and biochemically (Table 1, Fig. 1). All patients had normal levels of GH and/or IGF-I at the time when hyperprolactinaemia was first diagnosed (Fig. 2). The three acromegalic patients developed elevated serum IGF-I levels and abnormal OGTT within 29 to 60 months of dopamine-D2 agonist therapy. The average amount of dopamine-D2 agonist (parlodol) administered in patients 1, 2 and 3 was 5, 20 and 2.5 mg per day. Only in patient 1 were PRL levels normalised during treatment (Fig. 3). None of the three patients who developed acromegaly and/or elevated IGF-I levels received octreotide before the diagnosis of acromegaly was established clinically and biochemically. In two tumours only one of the antigens was present in the available material, and in the third hGH and prolactin were found in separate cell populations (Table 1).

The females with prolactinomas were significantly younger than the males (P < 0.006).

An additional five patients had significantly elevated IGF-I levels (Table 2). Two of these patients had a GH nadir > 1 mU/l during an OGTT (patients 4 and 6) without dopamine-D2 agonist therapy (Table 2). These five patients had no symptoms or signs of acromegaly.

**Acromegaly**

The mean (min-max) IGF-I level at diagnosis in 48 patients was 730 µg/l (268–1753) (Fig. 2). Seven out of 24 females had hyperprolactinaemia with a median (min-max) of 90 µg/l (27–494) (Fig. 1). Four out of seven patients had macroadenomas. Thirteen out of 35 males had hyperprolactinaemia with a median (min-max) of 47 µg/l (17–251). Ten out of 13 adenomas were macroadenomas. Neither PRL levels nor age differed when comparing males and females with acromegaly and hyperprolactinaemia.

**Prolactin levels, age and sex**

PRL levels were significantly higher in males with prolactinomas compared with males with acromegaly and hyperprolactinaemia (P < 0.002). There was no significant difference between females.

**Figure 1** (Left panel) Individual prolactin levels at first diagnosis in prolactinoma patients who developed acromegaly (○), in males (●) and in males whose PRL levels were >1400 µg/l (▲), in females (□) and in females whose PRL levels were >1400 µg/l (△). (Right panel) Prolactin levels in patients with acromegaly with hyperprolactinaemia. Males (●), females (□). Medians are indicated by horizontal bars.
Patients with acromegaly and hyperprolactinaemia were significantly older than patients with prolactinomas (47 (20–66) vs 32 (14–74) years) ($P < 0.005$). Females with acromegaly and hyperprolactinaemia were significantly older than females with prolactinomas (47 (31–66) vs 32 (14–74) years) ($P < 0.03$) but there was no significant difference between the ages of males with acromegaly and hyperprolactinaemia and those with prolactinomas (45 (19–67) vs 47 (20–66) years) ($P > 0.05$).

**Discussion**

We found that three out of 78 patients with prolactinomas developed acromegaly. We suspect that more patients could have developed acromegaly as 45 patients were treated with a dopamine-D2 agonist at the last visit and it has been found that GH levels, especially in patients with acromegaly and hyperprolactinaemia, are sensitive to dopamine-D2 agonists (8). Our findings emphasise the need for careful endocrine evaluation of prolactinoma patients including those with microprolactinomas (patient 3). The interval from onset of symptoms to diagnosis of acromegaly may range from 1 year to several decades (13). The interval in patients with hyperprolactinaemia with no initial acromegalic symptoms to the possible development of acromegaly in a subgroup of patients needs to be established in a large prospective study. The five patients who had only elevated IGF-I levels (Table 2) need to be followed annually to clarify the clinical importance of elevated IGF-I levels. Patients with acromegaly commonly show incomplete suppression, no suppression, or a paradoxical rise in GH during an OGTT. In two small series ($n = 13$ and $n = 30$ respectively) (14, 15), initial IGF-I concentrations in acromegals diagnosed by OGTT were shown not to overlap with those in control subjects. Thus an elevated IGF-I level in a patient with the appropriate clinical picture is diagnostic of acromegaly (16). This leads to the possibility of using a single IGF-I measurement for diagnosis (9). The routine use of serum IGF-I as a marker of GH activity in acromegaly is potentially very attractive for several reasons (9): (a) it involves a single serum sample; (b) IGF-I has a long half-life and therefore a stable serum concentration unlike GH; (c) it may be the ideal physiological marker of GH activity, as GH exerts most of its actions via IGF-I production; and (d) many treated acromegalic patients with GH $< 5$ mU/l continue to exhibit elevated IGF-I levels. During a 24-h profile the trough levels of serum GH were positively associated with raised IGF-I levels in acromegalics even when mean 24-h serum GH was $< 5$ mU/l (17). IGF-I levels are affected to some degree by the type and route of other hormone replacement therapy (e.g. with oestrogen) (9). In our study, however, the IGF-I changes could not be explained by oestradiol
therapy - none of the patients that developed increased IGF-I levels were treated with oestradiol.

The adenomas in patients with primary hyperprolactinaemia may be heterogenous (18). In a large study on transsphenoidal surgery on prolactinomas (176 microadenomas and 233 macroadenomas), Feigenbaum et al. (19) found that 50% patients had a chromophobe adenoma and 50% of these patients had macroadenomas. Interestingly, the preoperative PRL levels were similar in those 50 patients and in patients with histologically confirmed prolactinomas. Mixed PRL- and GH-secreting adenomas were found in an additional 31 female patients, one of these adenomas stained only for GH. No clinical features of acromegaly were noted in this patient. There was, however, no endocrinological data on the patients with mixed adenomas, focusing on GH hypersecretion (19).

In agreement with Feigenbaum et al. (19) we found that the females with prolactinomas were significantly younger than the males. We also found that females with acromegaly and hyperprolactinaemia were significantly older than females with prolactinomas ($P < 0.03$). There was, however, no significant difference between the males. All eight patients who developed elevated IGF-I levels and even acromegaly (three patients) were females. These data may suggest that in females with a possible heterogenous adenoma, the hyperprolactinaemia may lead to the first diagnosis because of the amenorrhoea-galactorrhea syndrome: in contrast in males acromegaly may lead to the first diagnosis. Our mean age for acromegalic patients of 47 years was in accordance with the mean age of 46 years reported by Bengtsson and coworkers (20). It is necessary to consider the possible changes in pituitary adenomatous secretion even during medical therapy. In 1984 Badawy and colleagues (21) published a case study where a patient with a prolactinoma developed acromegaly during 5 years of bromocriptine therapy and they suggested that comprehensive and periodic evaluation of hypothalamic–pituitary endocrine function is indicated in patients with hyperprolactinaemia. Two other case studies have reported findings in accordance with this study (22, 23). The problems with underdiagnosing acromegaly have been discussed before. Several years ago Pagesy et al. (24) reported that one has to be aware of apparently silent somatotroph adenomas. In that study the patients had weak signs of acromegalic features and they all had macroadenomas. Yamada and coworkers (25) have studied a clinically silent somatotroph adenoma. They suggest that the lack of clinical acromegaly in patients with elevated GH and IGF-I levels is due to the short duration of GH hypersecretion.

The role of dopamine in healthy adults and acromegalic patients is different. Dopamine is a weak stimulator of GH secretion in healthy adults, and L-dopa has been used for diagnosing GH deficiency (13). In acromegaly dopamine reduces GH levels in up to 25% of patients (13). We have found an increase in IGF-I levels in patients on dopamine-D2 agonist therapy as well as in patients without therapy. Are the increased IGF-I levels due to the effect of dopamine-D2 agonist therapy on the normal somatotroph cells? No, this is unlikely. On the other hand, Torring and coworkers (26) found no change in IGF-I levels in patients with hyperprolactinaemia where bromocriptine had normalised PRL levels.

In conclusion, our findings suggest that there may be a common group of patients with a pituitary adenoma and unsynchronised PRL and GH secretion. Some of these patients have clinical acromegaly at diagnosis and some patients will develop clinical or subclinical acromegaly. However, future studies are necessary to clarify the risk of developing acromegaly in patients with hyperprolactinaemia. We suggest an annual IGF-I measurement as a screening test. We are planning a prospective study on GH hypersecretion in patients with hyperprolactinaemia.

### References


15 Ho KY & Weissberger AJ. Characterization of 24-hour growth hormone secretion in acromegaly: implications for diagnosis and therapy. *Clinical Endocrinology* 1994 41 75--83.


