Acromegaly : treatment and follow-up : the Leiden studies

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Postoperative persistent thyrotrophin releasing hormone-induced growth hormone release predicts recurrence in patients with acromegaly

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Clin Endocrinol (Oxf) 2002; 56:313-319

SUMMARY

OBJECTIVE: To assess the predictive value of postoperative thyrotrophin releasing hormone (TRH)-induced GH responsiveness in relation to (late) postoperative outcome in patients in remission after surgery for acromegaly.

PATIENTS AND METHODS: One hundred and twenty-nine patients underwent surgery for acromegaly in our institution between 1977 and 1996. TRH tests and oral glucose tolerance tests (GTT) were performed and serum IGF-I concentrations were measured pre- and postoperatively and during follow-up. Criteria for postoperative remission were a mean serum GH concentration < 5 mU/l and/or serum GH after an oral glucose tolerance test < 1 mU/l immunofluorometric assay (IFMA) or < 2.5 mU/l (radioimmunosassay), together with a normal serum IGF-I concentration.

RESULTS: Preoperatively, the TRH-induced GH response was highly variable, with gradual overlap between 'nonresponders' and 'responders'. Arbitrarily defined as a doubling of serum GH concentration, 45.6% of patients were 'responders' to TRH. GH response after TRH injection was significantly correlated to the TRH-induced prolactin response but not to preoperative GH concentration or adenoma size. After surgery, remission was achieved in 83 of the 129 patients. Postoperative remission was significantly correlated to mean preoperative serum GH concentration and preoperative glucose-suppressed serum GH but not to tumour class. Seventy-one patients with early postoperative remission were followed without adjuvant treatment for a mean of 9.4 ± 0.7 years (range 0 – 23 years). Forty-one of these patients were TRH responsive as defined by at least doubling of the serum GH concentration preoperatively. Of the 71 patients, 12 developed recurrence of disease, as defined by insufficient GH suppression during oral GTT, and elevated IGF-I and mean serum GH concentration. Irrespective of the preoperative response to TRH, the initial postoperative TRH test was predictive of developing disease recurrence with a sensitivity of 75% and a specificity of 100% when an absolute GH increase of 3.75 mU/l was chosen to define paradoxical responsiveness. A stimulated GH 1.6 times basal was predictive of recurrence with a sensitivity of 83% and a specificity of 73%, and 2.1 times basal was predictive with a sensitivity of 75% and a specificity of 80%. None of the 32 patients with postoperative normalization of the preoperatively present TRH-induced GH response, defined as a postoperative GH increase < 3.75 mU/l, developed recurrence of disease, while all nine patients with a GH increase above this level developed recurrence of acromegaly.

CONCLUSION: To our knowledge this is the first report which addresses the value of early postoperative TRH-induced GH responsiveness in predicting late surgical outcome using receiver-operating characteristic (ROC) curves to redefine a postoperative paradoxical response instead of arbitrarily chosen criteria. An absolute postoperative GH response of more than 3.75 mU/l was associated with recurrence in all nine patients, while all 32 patients with normalization of previously paradoxical response are still in remission. Our findings from this study demonstrate that the TRH test is a valuable tool in the early identification of patients at risk of developing postoperative recurrence of acromegaly.

INTRODUCTION

IN ACROMEGALY, ABNORMAL GH RESPONSIVENESS to various pharmacological stimuli and hypothalamic releasing hormones, such as bromocriptine, TRH and GnRH, has been described (1). Of these, the 'paradoxical' GH response to TRH injection, observed in 50 75% of untreated acromegalic patients, has been investigated extensively but its underlying mechanism remains unclear. No clinical differences have been identified so far between patients with or without GH responses to TRH (2). Moreover, criteria for preoperative and/or postoperative paradoxical responsiveness to TRH are mostly arbitrarily chosen and various cut-off values have been used in different studies (3).

In the early 1980s, clinical follow-up studies of surgical series of patients with acromegaly suggested that a persistent response of serum GH to TRH after surgery indicated the presence of adenoma cells and might be predictive for regrowth of the adenoma and recurrence of acromegaly (4 – 7). More recently, others have found no recurrences in a selected population with postoperative persistent GH response to TRH (8). In a recent study on late outcome of surgery in acromegaly, with more than 10 years follow-up and the use of strict criteria, we reported a recurrence risk of 19% (9). As can be expected from the slow growth rate of pituitary tumours, in long-term studies (9,10) recurrence rates may be higher than those reported in short-term studies (11). Mild recurrent GH hypersecretion, not always clinically evident, can nowadays be treated effectively with medical therapy with concurrent reduction of the elevated mortality risk associated with this condition (12). Identification of early predicting risk factors for recurrence are required to optimize follow-up care. The aim of the present study was first to identify the value of the postoperative TRH-induced GH release in predicting disease recurrence in a large population of patients with acromegaly in remission after surgery, and second to identify the magnitude of GH increase with the best predictive value in order to redefine paradoxical responsiveness.

PATIENTS AND METHODS

Patients

A total of 129 consecutive patients who underwent transsphenoidal surgery for acromegaly in the Leiden University Medical Centre between 1977 and 1996 were studied. The diagnosis of acromegaly was based on characteristic clinical and biochemical features (elevated mean GH and insufficient suppression after oral glucose loading). Mean age at the preoperative evaluation was 46.3 ± 1.1 years. There were 71 men and 58 women. Twenty-nine patients had a microadenoma, 77 patients had a noninvasive macroadenoma and 23 patients had an invasive macroadenoma.

Treatment

All patients underwent transsphenoidal microsurgery performed by the same neurosurgeon (H.v.D.). Secondary treatment was given postoperatively only if mean GH levels remained elevated except for 12 prophylactically irradiated patients. This was in the form of external radiotherapy (40 – 50 Gy) or medical GH suppressive treatment, e.g. bromocriptine and later octreotide. Before 1985, prophylactic radiotherapy was given to 12 patients with a postoperative persistent TRH-induced GH response or a preoperative assumed incomplete tumour removal, as they were expected to be at high risk of recurrence. After 1985, no prophylactic radiotherapy was applied immediately after surgery and patients with persistent reaction to TRH were followed without adjuvant treatment.

Evaluation

Assessments were performed before and after surgery (7 10 days and 3 6 months postoperatively) and thereafter once yearly and included an oral GTT, a TRH-test, a GH day-profile and a serum IGF-I level (from 1985 onwards). The Hardy Wilson surgical tumour classification (13) was simplified into microadenoma (pIo), noninvasive macroadenoma (pIIa c) and invasive macroadenoma (IId,e, III, IV).

Tests

GH day-profile: serum GH levels were measured at 0800, 1130, 1630 and 2300 h. GTT: GH, glucose and insulin were measured at 0, 30, 60, 90 and 120 min following oral ingestion of 75 g glucose. TRH-test: GH, TSH and PRL were measured at 0, 20 and 60 min following i.v. injection of 200 µg TRH (Relefact TRH, Hoechst, Frankfurt am Main, Germany).

Assays

Serum GH concentration was measured before 1992 with an RIA (Biolab, Serono, Coissins, Switzerland) calibrated against WHO IRP 66/21 [detection limit 0.5 mU/l, interassay coefficient of variation (CV) < 5%; for conversion to µg/l divide by 2]. From 1993 onwards, we used a highly sensitive IFMA (Wallac, Turku, Finland), specific for the 22-kDa GH protein, calibrated against WHO IRP 80/505 (detection limit 0.03 mU/l, interassay CV 1.6 8.4% between 0.25 and 40 mU/l; for conversion to µg/l divide by 2.6). Serum IGF-I concentration was determined using an RIA available from 1985 onwards (Incstar, Stillwater, MN, USA) with a detection limit of 1.5 nmol/l and interassay CV below 11%. Normal values were expressed as age-related SD scores from normal values derived from 137 healthy controls (14,15). Serum prolactin concentration was measured with an IFMA (Wallac) with a detection limit of 0.04 µg/l, interassay CV 3.4 6.2% in the range from 3 to 80 µg/l (for conversion to mU/l multiply by 32). Serum TSH was measured by an IFMA (Wallac), detection limit 0.05 mU/l and interassay CV below 5% for the concentrations measured here.

Criteria for remission

Postoperative remission was defined as the achievement of a mean serum GH concentration below 5 mU/l (~2.5 µg/l) and/or a normal serum GH suppression during GTT as determined in healthy controls. Normal suppression was below 2.5 mU/l (1.25 µg/l) for the RIA and below 1 mU/l (0.38 µg/l) for the IFMA (14). As an early postoperative IGF-I concentration was not available in all patients, this was not used as a criterion for determining early postoperative remission. Postoperative testing was performed 7 – 10 days after surgery.

Criteria for recurrence

After early postoperative remission, recurrence was defined as an elevated serum IGF-I concentration, a mean GH concentration > 5 mU/l and/or an insufficient suppression of GH concentration after oral ingestion of glucose, and clinical signs and symptoms. Treatment for recurrence was given on an individual basis depending on the presence of clinical signs and symptoms. Patients with up to now untreated mild recurrent GH hypersecretion are monitored biochemically and clinically once yearly but specific treatment has not been given as yet.

Data analysis

The statistical software SPSS 9.0 (SPSS Inc., Chicago, IL, USA) was used to perform statistical analysis and Sigma Plot 5.0 (SPSS Inc.) was used for drawing the figures. In the pre-and postoperative assessment, logistic regression analysis and nonparametric tests were used to assess whether the presence of a reaction to TRH was related to patients' characteristics, such as age and gender, hormone deficiencies and tumour characteristics, such as tumour classification, basal GH concentrations, reactions to other stimuli and immunohistochemical findings (JMP®, SAS Institute Inc., Chicago, IL, USA). Patients considered in remission postoperatively were followed yearly and divided into two groups: those who remained in remission at the end of follow-up (group A) and those who developed recurrence during follow-up (group B). To assess the predictive value of postoperative GH responsiveness to TRH in relation to recurrence and to estimation of optimal cut-off levels, we used the $\chi 2$-test and receiver-operating characteristic (ROC) curves (SPSS 9.0, SPSS Inc.). Data are expressed using means ± SEM (range) unless specified otherwise. A P-value of < 0.05 was considered significant.

RESULTS

Preoperative results

Preoperative TRH testing was performed in 125 patients. The response of serum GH concentration 20 minutes after TRH injection was highly variable, irrespective of baseline GH concentrations (Fig. 1): in 22% of patients no increase in serum GH concentration was observed

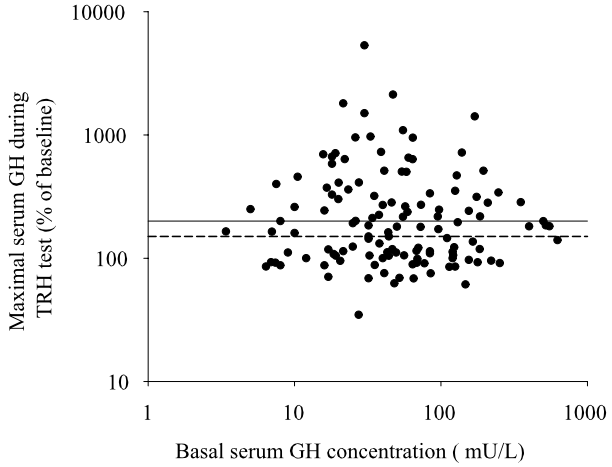

Figure 1. Scatter plot of the ratio of stimulated to basal serum GH concentration in relation to basal serum GH concentration. Both axes are scaled logarithmically. Solid line is the reference line for doubling of the GH concentration (ratio = 2.0); dotted line represents 50% increase in serum GH concentration (ratio =1.5).

during the TRH test, in 32% GH increased up to two times, in 28% two to five times and in 18% more than five times the baseline GH concentration. According to two frequently used criteria for paradoxical responsiveness (2,3,8,16,17), GH rose to 1.5 times the basal concentration in 70 patients (56%) and to twice the basal GH concentration in 57 patients (45.6%).

The increase in GH after TRH injection was significantly correlated with the increase in PRL after TRH injection (R = 0.416, P < 0.001) but not with the increase in TSH. No correlation was found between TRH-induced GH response and either preoperative mean GH concentration, baseline GH concentration or tumour class.

Early postoperative results

Postoperative remission was achieved in 83 patients (64%), of whom 12 underwent prophylactic radiotherapy and 71 were followed up without adjuvant treatment. The other 46 patients had persistent (biochemical) disease activity postoperatively. The early postoperative result (remission vs. persistent disease) was significantly correlated to mean preoperative serum GH concentration (P = 0.006) and to minimum serum GH during GTT (P = 0.03), but not to tumour size, to fractional increase (expressed as the ratio of the highest GH concentration reached during the test vs. basal GH concentration) during preoperative TRH testing (P = 0.07) or to absolute increase during preoperative TRH testing (P = 0.67). The remission rate was significantly higher in patients with preoperative doubling of serum GH during a TRH test compared to those with a lower response, i.e. 45 of 58 patients (78%) and 35 of 67 patients (52%), respectively (P = 0.005).

Follow-up of 71 patients in remission postoperatively (without adjuvant treatment)

Seventy-one patients who were in remission and not adjuvantly treated after surgery were followed up for a mean of 9.4 ± 0.7 years (range 0 23 years, median 8 years). Recurrent GH hypersecretion was noted in 12 patients during follow-up despite early postoperative normalization of GH suppression after GTT. To date, seven of these patients have received adjuvant treatment (Table 1).

The TRH-induced GH response during the first postoperative TRH test, irrespective of the preoperative GH responsiveness to TRH, was assessed for its value in predicting recurrences (Fig. 2a, ROC curve of absolute TRH-induced GH increase, and Fig. 2b, ROC curve of the ratio of GH response). An absolute increase in GH during TRH testing of > 3.75 mU/l (1.44 µg/l) discriminated between patients with recurrence of disease and those in long-term remission with a sensitivity of 75% and a specificity of 100%. A stimulated GH level 1.6 times basal was predictive of recurrence with a sensitivity of 83% and a specificity of 73% and 2.1 times basal was predictive with a sensitivity of 75% and a specificity of 80%.

All nine patients with a postoperative persistent TRH-induced increase in GH concentration of more than 3.75 mU/l developed recurrence and none of the 32 patients with postoperative normalization of the preoperative paradoxical GH response developed recurrence (sensitivity

Table 1. Clinical characteristics of patients with recurrences.

Patient no.	Tumor class	Preoperative mean GH (mU/L)	Preoperative GH response to TRH(mU/L)	Postoperative mean GH (mU/L)	Postoperative glucose-suppressed GH (mU/L)	Post-operative TRH test (mU/L)	Random GH (mU/L) (end of follow-up)	Suppressed GH (mU/L) (end of follow-up)	Duration of remission (years)	Adjuvant therapy
1	pII[a]	114	ND	4.3	1.0	3.5→12.0	11.6	5.0	4	None
2	pII[a]	435	250→840	0.5	0.5	0.5→6.6	12.6	7.1	3	OCT
3	pII[b]	255	175→550	4.0	0.5	2.5→21.0	5.3	1.0	1	RT
4	pII[0e]	15	68→320	2.7	<1.0	2.7→11.1	13.5	1.7	2	OCT
5	pIII[a]	45	ND	1.2	ND	2.0→7.0	5.8	5.5	3	RT
6	pI[0]	44	8→16	4.3	0.5	5.0→15.5	3.4	2.7	12	None
7	pIII[0]	18	19→135	5.3	0.5	4.0→8.8	3.7	1.2	6	None
8	pII[0]	39	40→40	1.6	0.5	2.5→2.5	7.1	4.2	2.5	OCT
9	pII[0]	40	44→64	2.0	0.5	1.5→2.5	2.4	1.5	6	None
10	pII[0]	218	125→440	2.4	0.5	2.0→7.0	9.2	8.4	10	Surg, OCT
11	pII[a]	229	180→165	5.2	0.5	3.8→2.7	3.1	1.6	9	None
12	pII[e]	76	54→270	3.2	1.4	2.2→6.2	3.6	2.2	2	None

Tumor size is based on the Hardy-Wilson classification. Mean GH concentration is calculated from four samples taken during daytime. OCT, octreotide therapy; RT, radiotherapy; Surg, repeat surgery; ND: not done. Normal values: mean GH concentration < 5 mU/L, glucose suppressed GH concentration <2.5 mU/L (RIA) or < 1 mU/l (IFMA). All postoperative glucose suppression tests and TRH-tests were analysed by RIA. In the follow-up to surgery, assays of patients 1, 3, 4, 5 and 12 were performed by RIA and of the other patients by IFMA.

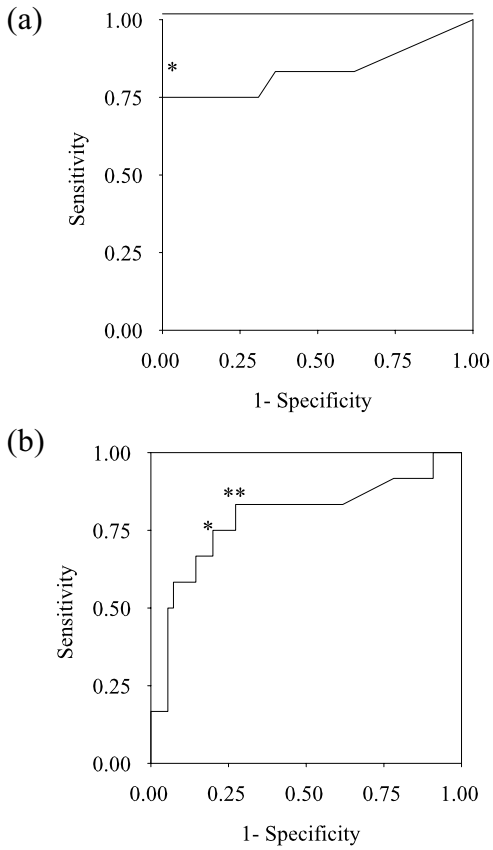

Figure 2. ROC curves of (a) absolute increase and (b) the fractional change in serum GH concentration after TRH injection. (a) Best cut- off point (*) increase of 3.75 mU/l (1.44 µg/l). (b) Cut-off points maximum increase (*) 2.1 times and (**) 1.6 times basal value.

and specificity 100% [ ]. Conversely, three of [0 patients without a G[response to [R[before and after surgery [nonresponders'[also developed recurrence of disease [1 0[[.

Eight patients followed up yearly, in whom stimulated G[concentration was twice the basal level or more but with absolute increases between 2.8 and [.5 m[[[1.1 – 1.[µg[[) are still in remission after 9.[± 1.0 years.

DISCUSSION

[he present study was conducted to assess the late outcome of initial successful surgery in patients with or without postoperative G[reaction to [R[. We report a high recurrence risk in patients with postoperative [R[-induced G[release in contrast to no recurrence in patients with disappearance of their preoperative positive response to [R[. [sing ROC curves, the criterion of an increase in serum G[concentration of more than [.[5 m[[[1.[[µg[[

20 minutes after injection of TRH was discriminatory in predicting recurrence and remission (sensitivity 75%, specificity 100%).

Several studies on the surgical treatment for acromegaly suggested a high recurrence rate in patients with a persistent response to TRH postoperatively, hypothesizing that this response indicated incomplete removal of the pituitary tumour (4 – 7). Two small studies reported higher recurrence rates in postoperatively responsive patients than have been generally reported, namely one of seven (14%) and two of eight patients (25%) (2,20). In contrast, Brockmeier et al. (8) did not find any recurrence during a mean follow-up of 7.7 years in 20 patients with persistent postoperative GH responses to TRH. Although they selected patients with at least 5 years of follow-up, this follow-up period may not be long enough for a recurrence to become biochemically evident (19). More importantly, their criteria for remission and recurrence of basal serum GH (< 5 µg/l) and glucose-suppressed GH (< 2 µg/l) were less strict than those currently used and might have failed to discriminate between remission, persistent disease and mild recurrent disease. In addition, in patients with low basal GH concentrations, a 50% increase during the TRH test, for example from 1 to 1.5 µg/l, might reflect spontaneous fluctuations of GH concentration. In other large series, in which the response to TRH is not mentioned, the overall recurrence rate after surgery was 6% after a mean of 5 years and 10% after 10 years (10,11). In our patient group, postoperatively in remission according to strict criteria and followed for more than 10 years, we reported a recurrence rate of 19% (9). This increasing recurrence rate with time emphasizes the importance of long-term (life-long) follow-up in each patient with acromegaly and the need to determine risk factors predictive for recurrence.

Most clinical studies have arbitrarily defined a paradoxical reaction as a GH response to TRH as more than 1.5 times or more than twice the basal values (3 – 5,17,21) or as a serum GH increase of more than 3 10 µg/l (about 6 – 20 mU/l) (2,3,5,6,22 – 24). The novel finding of our study is that an absolute GH increase of > 3.75 mU/l (1.44 µg/l) during the early postoperative TRH test is able to predict recurrence with a sensitivity of 75% and a specificity of 100%, while a stimulated concentration of 2.1 times the basal serum GH concentration had a lower specificity. In this study, patients with a preoperative TRH-induced GH concentration of more than twice the basal concentration were judged arbitrarily to be 'responders', although we observed a continuum in responsiveness when expressed both as an absolute increase and as a fractional response (Fig. 1). Other chosen cut-off values, however, did not change our results on remission and recurrence rates.

Although the mechanism of TRH-induced GH release remains to be elucidated, it seems to be a tumour-related phenomenon that is present in 50 75% of patients with acromegaly and can be reproducibly evoked in 'responders', albeit with variation in the magnitude of the GH response (25,26). In the present study, we observed a wide range of TRH-induced GH responses preoperatively irrespective of the basal serum GH concentration. The finding of no recurrence in patients with normalization (GH increase < 3.75 mU/l or < 1.44 µg/l) of a pre-

operative TRH response contrasting with the high recurrence rate in patients with persistent responsiveness (GH increase > 3.75 mU/l or > 1.44 µg/l) favours the idea of a clinical tumour marker.

In the present study none of the patients with normalization of preoperative paradoxical TRH response after surgery developed recurrence of disease. In contrast, others have reported the reappearance of paradoxical responsiveness postoperatively after initial normalization of the response and subsequent development of recurrence (2,20). No other study has reported a similar high recurrence rate in the (preoperative) responsive patient group (22%) compared to the nonresponsive patients (10%), although it failed to reach statistical significance (P = 0.2) possibly because of the small number of patients.

An interesting but unexplained observation was the significantly higher remission rate in those patients with GH response to TRH compared to nonresponders (78% vs. 52%). Another study (2) also observed significantly lower serum GH concentration after surgery in preoperative responders compared to nonresponders. Contrary to others, we found significant correlations between the TRH-induced GH response and the TRH-induced prolactin response (1). A highly significant correlation between the TRH-induced GH response and the growth hormone-releasing peptide (GHRP)-induced GH response was found in patients with active acromegaly (27), suggesting a common mechanism in GH release between GHRP and TRH via the phosphatidyl inositol protein kinase C pathway instead of the effect of GHRH which is exerted via the adenylate cyclase protein kinase A pathway. In this connection, Smals et al. (28) reported an inverse correlation between the response to TRH and to GHRH in acromegalic patients.

The identification of risk factors for the development of recurrence should result in useful tools for optimizing individual treatment and follow-up strategies. In our population the evaluation of a preoperative and a postoperative TRH test permitted the differentiation between 'nonresponders' with a recurrence risk of 10% and patients with a normalization of the response to TRH with no subsequent recurrences. In those patients with recurrence of disease, a repeatedly higher response of GH to TRH seems to precede the elevated serum GH and suppressed serum GH concentrations (data not shown) whereas patients without recurrence and a response below 3.75 mU/l do not demonstrate increases in GH responsiveness to TRH during follow-up. This observation suggests a slow increase in number of tumour cells after surgery, preceding the clinical relapse.

Pituitary tumours grow very slowly and recurrence rates from long-term follow-up studies (9,10) are expected to be higher than those observed in short-term studies (11). Since mild, barely clinically evident recurrences can now be effectively treated with adjuvant medical therapy with concurrent reduction of the elevated mortality risk, identification of risk factors for recurrence is required to optimize follow-up care. Although the pathophysiological mechanism of the paradoxical responsiveness of GH to TRH is unknown, our data demonstrate that the TRH test is a valuable tool in identifying patients at risk of recurrence of acromegaly.

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