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Does Treatment of Acromegaly Affect Life Expectancy?

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Previous studies have demonstrated a twofold to threefold increase in mortality in acromegalic patients largely due to increased cardiovascular disease, but also in some series due to increased malignant disease. In a retrospective analysis of 79 patients from one large hospital center in the United Kingdom, we sought to determine (1) whether the increased mortality persists and (2) what is the relationship between mortality and growth hormone (GH) levels achieved following treatment. Hospital records and death certificates were scrutinized and serum GH data collected from patients treated between 1967 and 1991. GH assessments were performed on average annually during follow-up evaluation and consisted of 3-hour measurements during waking hours in a GH day series. The average value was calculated from five readings. We used the lowest value, usually the most recent, for average GH achieved during the follow-up period. There were 29 males and 50 females, and no numerical difference between sexes was found in living and deceased groups. The mortality of the cohort was compared with that of the general population, and expected mortality was calculated from Office of Population Census Statistics data. The observed to expected ratio was determined. There were no differences between living and deceased groups in the proportion of subjects with hypertension, diabetes, or visual field defects at the time of diagnosis. Most patients were treated with radiotherapy ± bromocriptine as primary therapy. There was a marked shift to lower mean GH values with treatment such that 48 of 79 had values less than 10 mU/L. Those subjects with mean GH levels less than 5 mU/L had significantly lower serum insulin-like growth factor-I (IGF-I) values than subjects with values above this level. The observed to expected mortality ratios (with 95% confidence intervals in parentheses) were as follows: males, 2.55 (1.4-4.3), $P = .002$; females, 2.83 (1.6-4.8), $P = .001$; total, 2.63 (1.8-3.9), $P < .001$; lowest GH less than 10 mU/L, 2.01 (0.9-3.83), $P = .039$; and lowest GH less than 5 mU/L, 1.42 (0.46-3.31), $P = .28$. These results show that overall mortality in both males and females with acromegaly is still two to four times that of the general population. However, the important novel finding is that if GH levels of less than 5 mU/L can be achieved, there is no increased mortality. The median age of death (62 years) was similar to that found previously; 57% of deaths were due to vascular causes, 25% to respiratory disease, and 11% to malignancy. Small numbers of deaths precluded statistical comparison with the general population. The implication of these preliminary data is that if serum GH levels can be reduced to less than 5 mU/L by treatment, the long-term outlook for acromegalic patients is very good. These data need to be confirmed with a larger cohort of patients.

ACROMEGALY is an uncommon condition, with a prevalence estimated at 40 per million population.[1] A number of large series have now demonstrated that the condition is associated with increased morbidity and mortality.[1-4] These series suggest that acromegalic patients have between two and three times the mortality found in an age- and sex-matched control population drawn from England and Wales. The cause of these excess deaths is usually vascular, although increased mortality from respiratory and malignant pathology has also been reported.[1,2,4,5] Treatment, including surgical hypophysectomy, external beam irradiation, radioactive seed implantation, and more recently medical treatment with bromocriptine and octreotide, has not been shown to affect this adverse prognosis. Since treatment is usually required for symptomatic relief, decompression of the sella, or management of complications, there is no unselected series of untreated acromegalics for direct comparison with respect to mortality. In addition, none of the published series has related mortality to the effect of treatment on growth hormone (GH) levels. We have analyzed data retrospectively from North Staffordshire to determine (1) whether this poor outlook still persists, (2) the efficacy of treatment in reducing GH levels, and (3) the relationship between GH levels and mortality.

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SUBJECTS AND METHODS

Seventy-nine patients have been identified from hospital records between 1967 and 1991, with a preponderance of females, which has been noted in previous series. Fifty-one are alive and currently under follow-up evaluation, and 28 have died (Table 1).

Hospital records and death certificates were scrutinized for clinical details and GH data, as measured by a double-antibody radioimmunoassay. Before treatment, GH results are presented as the average of GH levels measured during a standard 50- or 75-g oral glucose tolerance test (OGTT). During follow-up evaluation performed approximately annually, an assessment of response to treatment was made by calculating an average of five GH measurements taken at 3-hour intervals during waking hours (day series). Follow-up data are then expressed as the lowest average GH day series achieved at any time during the follow-up period. In general, the lowest value is the most recent series. No GH data were available on 40% of the dead group at diagnosis or 25% of the alive group. This was due to the lack of a reliable assay at the time of diagnosis in these patients. During follow-up evaluation, only 16% of the dead group and 4% of the alive group had no assessment of GH secretion.

Statistical Methods

Characteristics of the dead and alive groups were compared using the chi-square test to analyze categorical variables and the Mann-Whitney *U* test for continuous variables. Correlation analysis between continuous variables was performed after ranking data from smallest to largest, using Spearman rank correlation analysis.

The mortality of the whole group was compared with that of the general population by methods previously described,[6] which are similar to two of the previous UK series.[1,4] The age and sex structure of the acromegalic population alive during each 5-year calendar period was calculated from 1941 to 1991, and the death rate for that period (derived from Office of Population and Census Surveys data) was applied to calculate an expected number of deaths. The total number of expected deaths for each period was used to provide an overall total against which to compare the observed mortality. Assuming that the observed number of deaths was Poisson-distributed, it is then possible to apply a one-sided test to see whether there was a significant increase in mortality in the acromegalic cohort. A similar method was used to compare defined subgroups of patients with the general population, such as those with GH levels of less than 10 mU/L.

Treatment Methods

The facilities locally available in Stoke-on-Trent during the major part of this study were largely responsible for the decision to treat most of the patients with external beam radiotherapy, with or without bromocriptine since 1974. All our patients received 4,500 rads over a 5-week period. Smaller numbers have undergone surgical hypophysectomy, and most of these have required additional treatment either in the form of external radiotherapy or bromocriptine. Very few patients have remained untreated, and this is usually as a result of age or coincident medical problems (Table 2).

Table 1. Subject Characteristics at Diagnosis

	Alive (n = 51)	Dead (n = 28)	Total	*P*
Sex (M/F)	15/36	14/14	29/50	.12 (male *v* female)
Age at diagnosis, median (range)	49 (22-79)	52 (27-70)	50 (22-79)	.36
Hypertension	9 (17.6%)	4 (14.3%)	13 (16.5%)	.96
Diabetes	6 (11.8%)	2 (7.1%)	8 (10.1%)	.82
Visual field defects	2 (3.9%)	5 (17.9%)	7 (8.9%)	.10

Table 2. Treatment Methods

Treatment	Alive	Dead	Total
Radiotherapy ± bromocriptine	33	17	50
Surgical hypophysectomy ± bromocriptine	4	3	7
Hypophysectomy and radiotherapy	4	0	4
Multiple treatment modalities	3	2	5
Bromocriptine alone	3	1	4
Radioactive implants	2	1	3
Nil	2	4	6

RESULTS

GH Secretion Pretreatment and Posttreatment

GH data pretreatment and posttreatment for the group as a whole are shown in Fig 1. Pretreatment data are represented by the mean GH level during a standard OGTT, and posttreatment values are the lowest average GH level achieved during the follow-up period. There is a marked shift in the distribution of GH values to the lower GH bands following treatment. Insulin-like growth factor I (IGF-I) secretion has also been assessed since 1990, and results are shown where available in Fig 2 (n = 41). The lowest IGF-I recorded is related to the lowest GH day series. Those patients reaching a GH level of less than 5 mU/L had significantly lower IGF-I levels than the other two groups ($P < .05$, Wilcoxon rank-sum test).

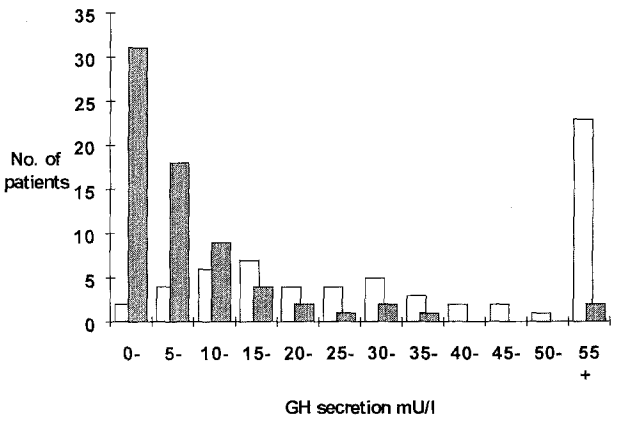

Fig 1. Distribution of GH secretion (□) pretreatment with values given as the mean of five levels measured during a standard OGTT and (▨) posttreatment values, which represent the average of five GH levels taken during the day. The lowest average value achieved during the course of the patients' follow-up period is shown in the distribution.

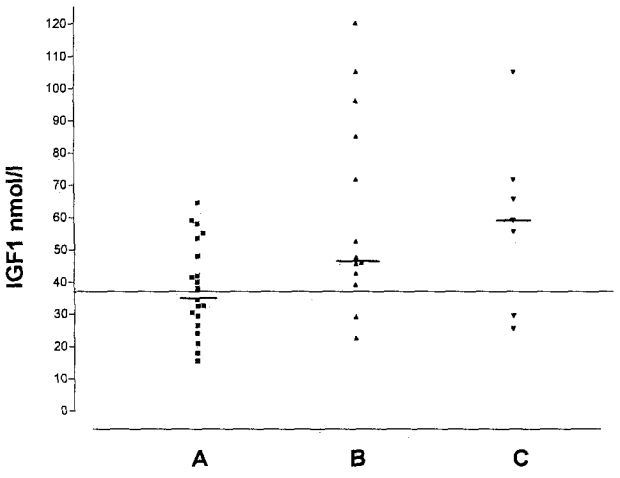

Fig 2. Lowest IGF-I level recorded in three groups of patients defined by the lowest average GH value achieved. (A) Those patients who achieved a lowest average GH value of less than 5 mU/L; (B) between 5 and 10 mU/L; (C) greater than 10 mU/L. Individual values and median are shown.

Mortality in Acromegaly

The mortality of the cohort was compared with that of an age- and sex-matched control population by methods previously described. There was a highly significant increase in the observed deaths as compared with the expected number for males, females, and the group as a whole. Our data suggest that there is between two and four times the mortality found in the general population (Table 3).

Effect of GH Reduction on Mortality

The mortality of those patients with a GH secretion of less than 10 mU/L was compared with that of the general population by methods similar to those previously described. This value was chosen since it is that below which several surgical series have arbitrarily defined a "cure".[7,8] More recent series have used lower values to define successful outcome,[9-11] and in view of this, patients with GH levels less than 5 mU/L were also separately assessed. The results are shown in Table 4 and indicate that mortality is increased relative to the general population, even in those patients achieving GH levels previously associated with a cure.[7,8,12] However, those with a lowest average GH not exceeding 5 mU/L demonstrated a survival similar to that of the general population. To determine whether this particular subgroup contained patients with mild disease and lower GH levels throughout the course of the disease,

Table 3. Mortality in Acromegaly Compared With That of the General Population

	n	Observed Deaths	Expected Deaths	Ratio of Observed to Expected (95% CI)	*P* (one-sided)
Male	29	14	5.5	2.55 (1.4-4.3)	.002
Female	50	14	4.94	2.83 (1.6-4.8)	.001
Total	79	28	10.44	2.63 (1.8-3.9)	<.001

Abbreviation: CI, confidence interval.

Table 4. Mortality in Acromegaly According to GH Secretion

Group	n	Observed Deaths	Expected Deaths	Ratio of Observed to Expected (95% CI)	*P* (one-sided)
Lowest of all GH day series <10 mU/L	48	9	4.48	2.01 (0.9-3.83)	.039
Lowest of all GH day series <5 mU/L	31	5	3.52	1.42 (0.46-3.31)	.28

pretreatment GH during a standard OGTT was compared with the lowest day series achieved (Fig 3). There is a highly significant correlation ($P < .01$) between the two, suggesting that those patients achieving lower GH values following treatment tend to be those having low GH levels before treatment. In addition, comparison of those patients achieving a value of less than 5 mU/L to those failing to do so with respect to pretreatment GH secretion (Fig 4) reveals that although there is a large overlap between the two groups, the former does tend to have lower levels of pretreatment GH secretion, although the difference does not quite achieve statistical significance ($P = .06$).

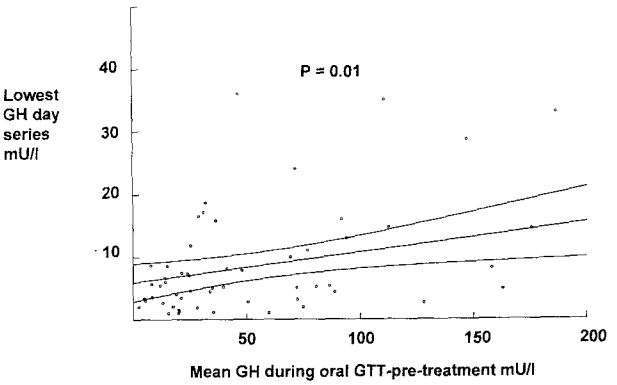

Fig 3. Correlation of the mean pretreatment GH level during a standard OGTT with the lowest day series achieved during the course of the patients' follow-up period. The linear regression line with 95% confidence limits is shown.

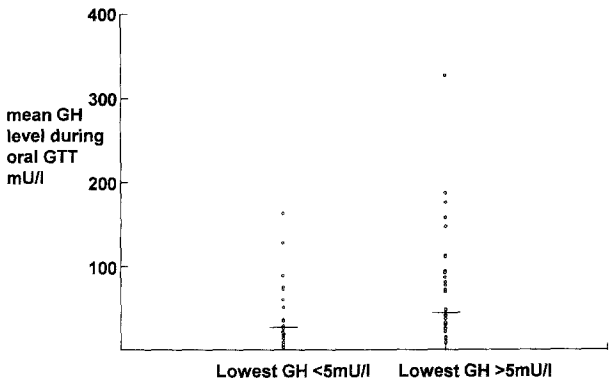

Fig 4. Comparison of mean pretreatment GH levels during a standard OGTT in patients who either did or did not achieve a lowest day series of less than 5 mU/L. Median values are shown.

Table 5. Cause of Death in Acromegaly

Causes of Death (%)	Wright et al[4] 1970	Alexander et al[1] 1980	Nabarro[3] 1987	Bengtsson et al[2] 1988	This Study
Vascular	38.5	60	55	47	57
Respiratory	18	15.5	6	—	25
Malignant	18	15.5	23	24.5	11

Cause of Death

Causes of death are shown in Table 5 and compared with the other four published series. The small numbers precluded any comparison with the general population. The median age at death was 63 years (range, 42 to 81).

DISCUSSION

It is well recognized that acromegaly is associated with increased mortality.[1,2,4] Three of the four large series published in the last 20 years have demonstrated a significant increase in mortality. Only one series has failed to confirm these findings, and even in this study there was an excess mortality in males under the age of 55 and females of all ages.[3] Overall, these studies suggest that mortality in acromegaly is approximately double that found in the general population. The cause of death is most commonly vascular, but significant increases have been reported for both respiratory[4] and malignant causes.[2]

The diagnosis of acromegaly is rarely difficult, based as it is on incomplete suppression of GH levels following glucose challenge. However, follow-up assessment is more difficult, and much controversy remains over the definition of a biochemical cure. Many surgical series[8,13,14] have used basal GH levels of less than 10 mU/L as a convenient cutoff, but it is not clear on what basis this value was chosen. However, this value continues to be cited as representing a cure following surgical treatment.[12] More recently, increasingly stringent definitions of cure based on GH levels have been used.

Both Lamberts et al[10] in 1988 and Ho et al[9] in 1990 have suggested that serum IGF-I levels should be normalized and basal GH levels reduced to less than 6 mU/L before assuming a cure. Further support is provided by Lindholm et al,[11] who presented 13 patients achieving a cure on clinical grounds, all of whom had basal GH levels of less than 5 mU/L. However, no series has yet shown that reduction of GH levels to less than 5 mU/L can improve the poor prognosis still associated with acromegaly. Despite the fact that 60% of our cohort achieved an average GH level of less than 10 mU/L, the mortality of the group remains double that of age- and sex-matched controls.

However, we have shown that suppression of GH levels to less than 5 mU/L reverses the long-term poor outlook and reduces mortality to that found in the general population. One possible explanation for this finding is that those patients achieving GH values of less than 5 mU/L are a subgroup with milder disease, reflected in lower GH levels both pretreatment and posttreatment, who might be expected to have a better outlook at the start. This argument is supported by the fact that these patients do tend to have lower pretreatment GH levels, although there is a considerable overlap between groups.

However, it remains clear that to achieve GH secretion of less than 5 mU/L, the majority of patients will require effective treatment, which is indicated in any case for symptomatic relief and often chiasmal decompression. However, the data do support the view that the patients most likely to achieve this target are those with lower initial GH secretion. In addition, a study of 151 patients from Auckland, New Zealand, between 1964 and 1989 has examined factors associated with outcome defined as death, major complications, or minor/no complications.[15]

The duration of the follow-up period and estimated duration of acromegaly did not influence outcome, although the dead subgroup had a significantly longer estimated duration of symptoms before diagnosis than those with minor or no complications. Although GH at diagnosis was not significantly higher in the dead subgroup, it was almost twice that in the other two groups. If the data had been analyzed as dead versus alive subgroups, it is likely that there would have been a significant difference, as indeed it was in our own study.[16] Nevertheless, the last known GH value was six times higher in the dead subgroup than in those alive with either major or no complications. The Auckland results would therefore corroborate our own conclusion that successful treatment is important for the long-term outcome in acromegaly.

The introduction of dopamine agonists in the mid-1970s does not yet appear to have had any impact on this adverse prognosis. This may be related to the inability of bromocriptine to reduce GH secretion into the normal (<10 mU/L) range in all but a few patients.[17] The development of the long-acting somatostatin analog octreotide may be a more effective alternative in the future.

Trials have already shown that it is capable of reducing GH secretion to less than 10 mU/L in 46% of patients,[18] as opposed to 14% with bromocriptine.[17] Since it appears that suppression of average GH secretion to at least below 5 mU/L may be necessary to reverse the adverse prognosis, it is perhaps of greater interest that octreotide was able to reduce average GH secretion to less than 4 mU/L in 20.8% of 165 patients in the same study.[18]

The reasons for the poor outcome of treatment are not clear. Some series have demonstrated a relationship with the presence of clinical diabetes[4] and hypertension.[1] We were unable to confirm these findings, although this may be due to small numbers. Bengtsson et al[2] (1988) similarly could find no association in a larger series. In New Zealand, the diagnosis of acromegaly was estimated to reduce survival by approximately 10 years, and this was significantly reduced by the presence of cardiac disease and diabetes mellitus at diagnosis.[15]

In conclusion, our long-term data confirm increased mortality, largely from vascular causes, in acromegaly. Patients who have died secreted more GH both before diagnosis and during the follow-up period. Our data show that suppression of GH secretion to below 5 mU/L improves the adverse prognosis and increases life expectancy toward normal.

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