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The role of cumulative growth hormone exposure in determining mortality and morbidity in acromegaly: a single centre study

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Abstract
Purpose Acromegaly has traditionally been associated with significant mortality and cardiovascular morbidity. The aim of this study was to assess the overall mortality and improvement in mortality and morbidity in acromegaly and correlate these with cumulative growth hormone exposure.
Methods All patients treated for acromegaly at our centre until 2012 were analysed in this retrospective observational study. Baseline demographic details such as age at diagnoses, radiological features and pituitary status were obtained on these 167 patients. Cumulative GH levels (GHy) were calculated as a sum of average of GH readings in consecutive years. Mortality rates and development of new diabetes, hypertension and cardiovascular events (stroke, congestive cardiac failure and ischaemic heart disease) were assessed.
Results The SMR for overall cohort was 1.6. There has been a significant improvement in SMR over the past two decades (SMR until 1992 2.5; SMR since 1992 1.0). Cumulative GH exposure was significantly high in patients who died (35.2 vs 24.1, $p < 0.01$) and in those with incident metabolic or vascular events during follow up (51.6 vs 24.4, $p = 0.0001$). The cardiovascular event rate of the 'new' cohort was significantly better than the 'old' cohort (8.0 vs. 29.1 %, $p < 0.001$).
Conclusion There has been significant improvement in mortality and morbidity associated with acromegaly, in the setting of routine care in a specialized endocrine unit. Early and effective treatment to 'control' acromegaly could reduce GH exposure and hence vascular comorbidities.

Keywords Acromegaly · Mortality · Cumulative growth hormone

Introduction

Acromegaly is an endocrine disorder characterized by autonomous over production of growth hormone (GH), usually from an adenoma of the pituitary gland. It is a rare disorder and has an estimated incidence of about 4–6 per million per year [1]. GH excess is associated with significant morbidity, including hypertension, diabetes, cardiovascular disease and sleep apnoea, apart from hypopituitarism and visual field defects due to the adenoma itself [2]. Acromegaly had been traditionally associated with significant excess mortality in comparison to the general population up to three decades ago, predominantly due to limited or no treatment options [3, 4]. Radiotherapy was the common first line of treatment and the immediate outcomes were not satisfactory [3]. Wider availability of transsphenoidal surgery in the 1970s made this the preferred and most successful treatment option, with good immediate and long term outcomes [5, 6]. The availability of Somatostatin analogues during the 1980s helped to improve outcomes further, as an adjunctive or preoperative treatment option for achieving control of acromegaly [7]. Availability of better imaging techniques such as MRI,

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newer drugs such as Pegvisomant and newer treatment modalities such as stereotactic radiotherapy, have helped to control the disease better [8, 9].

Several studies have reported on increased mortality in acromegaly patients, with standardized mortality ratio (SMR) varying from 1.3 to 3 [10–13]. A meta analysis in acromegaly recently showed increased all-cause mortality in patients with acromegaly in comparison to general population, despite surgical treatment [14]. Several factors have been associated with the increased mortality—increased GH, with the view that decreasing GH reverses the increased mortality [10, 12, 13, 15]; IGF-1 normalization, with some supporting [16, 17] and some disputing evidence [1, 18]; external beam radiotherapy [10, 19]; development of hypopituitarism [19, 20]. The limitations of the 'latest' GH levels in predicting mortality and morbidity have been highlighted recently [21, 22] along with the usefulness of cumulative GH exposure and time-dependant GH levels [21].

The results of an internal audit done from our centre was published in 1993 analysing data on 79 patients and showing an SMR of 2.68 [13]. This study showed that acromegaly was still associated with increased mortality but reduction of random GH to <5 mU/L (<2.0 ng/mL) levels improved the survival rates. This GH target was confirmed in several larger studies and was initially adopted in international consensus guidelines, although subsequent guidelines revised this downwards to 1 ng/mL (2 mU/L) [23].

The aim of this study was to evaluate (1) the overall mortality and morbidity associated with acromegaly over the past six decades (2) the role of cumulative GH exposure in mortality and morbidity and (3) improvement in mortality and long term outcomes over the last two decades by comparing with data published by Bates et al. [13] by dividing them as two cohorts; 'Old' (pre-1993) as published by, with all biochemical and clinical details *limited up to 1993* and 'New' cohort (post-1993 to end of 2012). The choice of 1993 was entirely arbitrary, and was not related to any major changes in management or treatment at our centre; however this did result in two cohorts of very similar size.

Patients and methods

A retrospective analysis of all patients treated with acromegaly since the inception of pituitary clinic at our tertiary referral centre in 1960s was conducted. Data for this analysis was limited to information collected retrospectively as part of normal clinical care and all information was anonymised. Ethics committee approval was not required as this was performed as an observational audit.

Data was derived from review of case notes, previous clinical letters, computer based pathology reports and biochemistry results and reviewing the local acromegaly database until December 2012. 167 patients had been registered at our centre. Cases referred with clinical suspicion of acromegaly were investigated and had a firm diagnosis based on accepted criteria (Lack of GH suppression to <1 mcg/L after oral glucose loading). IGF-1 was available as a diagnostic test since 1989 at our centre. The last available random GH measurement at our centre was considered as the latest GH level.

Endocrine evaluation

GH levels were measured by in-house RIA since early 1970s. Baseline value on the 2 h-75 g-OGTT was used as the initial GH measurement for statistical analysis. For follow-up, annual GH levels were taken from one of the following that was available: mean of GH day curve, mean of the GH values on 2 h-OGTT or a random GH (mean of random GH if more than one value available in a calendar year). All GH measurements were standardized to mcg/L; measurements before 2009 were reported in IU/L and a multiplying conversion factor of 0.33 was used since this was the equivalence with the assays and GH standards used in the study. Control was deemed to have been achieved if two consecutive GH values from random samples or mean of GH day profile or mean of GH values on OGTT were <1.7 mcg/L (equivalent of 5 IU/L) as this was the cut-off widely reported in mortality studies in literature as well as the previous study from our centre [13, 16].

IGF-1 was measured using an in-house RIA with acid ethanol extraction. All values were standardized to nmol/L; values in mcg/L were converted by multiplying conversion factor of 0.13. The previously published article from our centre did not have any data on IGF-1. Age and sex adjusted values were used to define control with standard values being 25–64 nmol/L at age 16–20 years, 14–48 nmol/L at age 21–30 years, 13–37 nmol/L at 31–45 years and 8–32 nmol/L if aged >45 years. Control was deemed to be achieved if two consecutive IGF-1 levels were within range. GH normalization was used as the criteria to establish adequate control, however for patients on Pegvisomant, normalization of IGF-1 was considered as the only criterion for control.

Cumulative GH levels were calculated as a sum of mean of annual GH levels for all the years of follow up, similar to the model published recently [21]. An average of GH levels in two consecutive years gave the average GH level for that duration-year. For example, if a patient had GH levels of 10 and 20 mcg/L in successive years, cumulative GH level would be 15 GH-year (GHy) for that one year. A similar average was then calculated year on year and added to give the cumulative GHy.

Hypopituitarism was defined as biochemically proven deficiency of at least one endocrine axis. The hypothalamo-pituitary–adrenal axis was deficient if the peak cortisol response to short Synacthen testing was <550 or <500 nmol/L after insulin stress testing, as per local hospital guidelines. The thyroid axis was deficient if the free T4 was below the range and TSH inappropriately normal or low. Serum testosterone being below the local reference range with a normal prolactin defined hypothalamo-pituitary–gonadal axis deficiency in male. In females, deficiency of this axis was defined if FSH was inappropriately low in post-menopausal female or amenorrhoea with normal prolactin in a pre-menopausal female.

Development of new diabetes, hypertension or cardiovascular events (ischaemic heart disease, congestive cardiac failure or stroke) were considered as significant cardiovascular events (CVE) contributing to morbidity from acromegaly.

For the purpose of sub-analysis, the cohort was divided into 2 groups: 79 patients who had been included in the Bates et al. paper in 1993 and this group was labelled as 'Old' cohort; 88 further patients had been managed since that publication and these were classified as 'New' cohort. For the purpose of sub-analysis, relevant morbidity and mortality data *was truncated up to end of 1992* for the 'old' cohort.

Statistics

Numerical data were analysed and presented as medians because of the skewed distribution. Comparisons of medians was analysed by Mann–Whitney U test and proportions using Fishers exact analysis with 2×2 contingency tables. A $p < 0.05$ was considered to be statistically significant. Internal analysis was performed by univariate and multivariate Cox regression analysis. Survival probability by time since diagnosis was plotted as Kaplan–Meier curves and differences in survival probabilities were tested using a log-rank test. Standardized mortality ratios (SMR) were calculated as the observed over the expected number of deaths using Stata statistical software. The expected number was derived by multiplying age (5-year bands), sex and calendar year (1-year bands) stratum specific death rates from the general population of England and Wales to the person-years at risk in each corresponding age, sex and calendar year specific stratum in the cohort and then summed across the strata.

Results

The median age at diagnosis for the entire cohort was 47 years (19–79). Random GH at diagnosis was 7.8 mcg/L (1–541) and random IGF-1 at diagnosis was 96 nmol/L (n = 66, range 18.3–615). Pituitary imaging (including MRI, CT scans, skull radiographs) showed microadenomas in 10.1 %, intrasellar macroadenomas in 75.5 % and macroadenomas with extrasellar extension in 3.6 % at diagnosis. 5.4 % had normal pituitary morphology. Hypopituitarism was present in 11.4 % at diagnosis; diabetes in 13.2 % and hypertension in 19.2 %. Transsphenoidal surgery was done in 56.3 %, radiotherapy in 50.3 % and pharmacotherapy in 55.1 % with use of SSAs in 25.2 % and dopamine agonist in 54.5 %. Median duration of follow up was 111 months (1–541).

Overall cohort-mortality

The overall SMR was 1.6 (CI 1.3–2.0, $p < 0.001$) for the entire cohort at our referral centre. A multivariate Cox regression analysis performed on the dataset demonstrated that treatment with radiotherapy (OR 4.3, CI 1.5–12.0, $p = 0.01$) and >3 pituitary hormonal axes affected after diagnosis of acromegaly (OR 4.2, CI 1.4–12.7, $p = 0.03$) was significantly associated with higher mortality and normalization of GH with reduced mortality (OR 0.3, CI 0.1–0.5, $p = 0.01$). Other factors included in the analysis, such as gender, age at diagnosis, GH at diagnosis, hypopituitarism at diagnosis and cumulative GH exposure did not show reach statistical significance. Medical therapy was not included in this analysis as the type and duration of medication used was quite variable in routine clinical practice.

Comparing the 67 patients who had died so far with the 100 who are under active follow up (Table 1), the median age at death was 71 years (43–88). GH at diagnosis, latest GH and IGF-1 were not significantly different between the two groups. Use of medical therapy was not different (55.2 vs 54 %, p = NS); however radiotherapy was more commonly used in those who died (68.7 vs 38 %, $p = 0.0001$). Cumulative GHy overall (35.2 vs 24.1, $p = 0.008$) and GHy till control of acromegaly (29.4 vs. 16.4, $p = 0.007$) were significantly higher in those who died. The duration to cure was longer, and the proportion with inadequate control of the disease higher in those who died. The risk of new occurrence of DM and HT were similar, but CVE rates were higher; and the duration to develop one of these was much shorter in those who died (45 vs. 154 months, $p = 0.007$).

Overall cohort-morbidity

Of the entire cohort, 57 patients had new development of DM, HT or CVE during follow up of acromegaly (13 DM, 33 HT, 29 CVE). On comparing the cohort of patients who developed incident complications with those who did not (Table 2), GH at diagnosis and latest GH were comparable;

Table 1 Comparison between died and survivors of the entire cohort

	Died Median (Range)	Survivors Median (Range)	*P*
N	67	100	
GH at diagnosis (mcg/L)	7.2 (1–200.0)	8.0 (1.6–130.0)	NS
Latest GH (mcg/L)	1.4 (0–120.0)	0.4 (0–70.0)	NS
Cumulative GH (GHy)	35.2 (2.8–397.3)	24.1 (2.3–758.0)	0.0083
Cumulative GH till control (GHy)	29.4 (1.6–397.3)	16.4 (1.7–757.3)	0.0071
Latest IgF-1 (nmol/L)	26 (5–95)	27.0 (1.4–103)	NS
Hypopituitarism at diagnosis	37.3 %	35 %	NS
Radiotherapy	68.7 %	38 %	0.0001
Medical therapy	55.2 %	54 %	NS
Control achieved	52.2 %	81 %	0.0001
Duration to achieve control (months)	53 (5–482)	29 (1–491)	0.070
Risk of new DM	10.5 %	6.0 %	NS
Risk of new HT	23.9 %	17 %	NS
Risk of new CVE	28.4 %	10.0 %	0.032
Time to event (months)	45 (1–393)	154 (2–384)	0.007

GHy, Growth hormone years; DM, diabetes; HT, Hypertension; CVE, cardiovascular events; NS, not significant

however the cumulative GH exposure (51.6 vs 24.4, $p = 0.0001$) and GH exposure till achievement of control (49.7 vs 17.8, $p < 0.01$) were significantly higher. Though the proportion of patients who achieved control was comparable (68 vs 70 %), the duration to achieve this control was significantly longer in the patients with incident complications (73 vs 34 months, $p = <0.05$).

Old versus new cohort

A sub-analysis was performed comparing the data already published from the 'Old' cohort by Bates et al. [13] with the 'New' patients who have been diagnosed and treated since that publication. Baseline data on the two cohorts are summarized in Table 3. The age at diagnosis (median 50.9 vs 49.3 years) and GH at diagnosis (median 9.0 vs 6.7 mcg/L) were comparable between the two groups. The prevalence of pre-existing comorbidities and hypopituitarism at diagnosis were again comparable between the two groups. Macroadenomas were more common in the 'old' cohort and microadenomas in the 'new' cohort. The proportion of patients who had surgical treatment was significantly higher in the 'new' cohort (81.8 vs 27.8 %, $p < 0.0001$), whereas it was the opposite with radiotherapy (23.9 vs 79.8 %, $p < 0.0001$) and medical therapy (45.5 vs 64.5 %, $p = 0.02$). The proportion of patients who achieved biochemical control of acromegaly was significantly lower in the 'Old' cohort (43.0 vs. 78.4 %, $p < 0.0001$) and the duration to achieve this was also significantly longer (40 vs 18 months, $p < 0.05$; Table 3).

Mortality

28 patients had died in the 'Old' cohort in comparison to 12 deaths in the 'New' cohort, showing a 60 % relative risk reduction in all cause mortality. The survival probability of the two cohorts is shown on the Kaplan–Meier survival estimates (Fig. 1) showing better survival rates in the 'New' cohort ($p < 0.01$). The overall mortality observed in the 'new' cohort was comparable to that expected in the general population (SMR = 1.0, 95 %CI 0.6–1.8; Table 4).

Of the 79 patients from the 'old' cohort followed up until end of 2012, a further 27 patients had died.

We analysed the two cohorts separately by comparing the patients who had died with those on active follow-up.

Table 2 Comparison of patients with incident complications due to acromegaly (DM, HT or CVE) with those without development of complications

	Patient with incident complications Median (SD) (Range)	Patients without incident complications Median (SD) (Range)	*P*
N	57	110	
GH at diagnosis (mcg/L)	9.1 (35.8)	6.3 (25.4)	NS
	(1.4–200)	(1.0–130.0)	
Latest GH (mcg/L)	1.3 (16.6)	1.1 (7.6)	NS
	(0.0–120.0)	(0–70.0)	
Cumulative GH (GHy)	51.6 (67.1)	24.4 (84.1)	0.0001
	(2.3–397.3)	(2.7–758.0)	
Cumulative GH till cure (GHy)	49.7 (68.7)	17.8 (84.6)	0.0063
	(2.4–397.3)	(2.5–757.3)	
Control achieved	39/57	77/110	NS
Duration to control (months)	73	34	0.018
	(1–273)	(2–482)	

GHy, Growth hormone years; NS, not significant

In the 'Old' cohort (Table 5), the cumulative incidence of DM, HT and CVE was statistically much higher in patients who died and the time span to develop these were much shorter showing the intensity of the disease, though this was not statistically significant. The cumulative GHy exposure was also higher in those who died, though this again was not statistically significant. The proportion of patients in whom disease control was achieved was much lower among those who died (21.5 vs. 53.0 %, $p = 0.009$). In the 'New' cohort (Table 6), the cumulative GH, GHy till cure, cumulative incidence of DM, HT and CVE and the time to develop these were similar between those who died or continued on treatment. The cumulative GH of those patients who died in the 'new'cohort was lower than the survivors; this is mainly because of the shorter duration of follow up among these patients. The duration of follow up of patients who died in the 'new' cohort was much shorter than those in the 'Old' cohort (38 vs 85 months, $p =$ NS).

Morbidity

The risk of occurrence of new onset of diabetes (6.3 vs 3.4 %, $p =$ NS) and hypertension (16.5 vs 10.2 %, $p =$ NS) were similar between the two groups. The risk of developing hypopituitarism during follow up period was higher in the 'Old' cohort (45.6 vs 28.4 %, $p < 0.05$). The risk of CVE was significantly higher in the 'Old' cohort (29.1 vs. 8.0 %, $p < 0.001$). Cumulative GHy exposure of the 'Old' cohort was significantly higher than the 'New' cohort (48.0 vs. 16.5 GHy, $p < 0.001$). The time-to-event analysis also demonstrates that 'Old' cohort developed these comorbidities within a shorter duration than the 'New' cohort (23 vs 65 months, $p < 0.05$; Table 3).

Discussion

This retrospective analysis of patients with acromegaly clearly demonstrates that the overall mortality associated with acromegaly remains higher than general population; but there has been a significant reduction in the SMRs over the recent decades and the current mortality rates are comparable to the general population. The cumulative growth hormone exposure could be the key determinant for mortality and morbidity associated with acromegaly, and could be a key parameter to target and risk-stratify patients during follow up.

Various studies have assessed mortality in acromegaly in the past. All of the studies had demonstrated that the mortality rate associated with uncontrolled acromegaly is high [3, 11, 13, 24, 25]. However reports on improvement of mortality have been variable, with most studies showing improved survival rates with reduction in GH levels [26] or normalization of GH level [1, 12, 17, 27]. The delay from the development of symptoms and the initial referral and diagnosis has decreased considerably, which will undoubtedly improve outcomes [28]. Further, conventional radiotherapy is well documented as an independent risk factor for mortality and the decreasing frequency of usage of conventional external beam radiotherapy in recent years would reflect on mortality improving (as has been noted in our 'new' cohort) [10, 28]. A study published from Canada

Table 3 Comparison between 'new' cohort and 'old' cohort with data truncated up to 1992

	'Old' cohort (up to 1992) Median (Range)	'New' cohort 1992–2012 Median (Range)	*P*
N	79	88	
Male	36.7 %	53.4 %	<0.05
Age at diagnosis (years)	50.9 (22–79)	49.3 (19–76)	NS
GH at diagnosis (mcg/L)	9.0 (1.6–200)	6.7 (1.6–130)	NS
Microadenoma	1.3 %	18.2 %	<0.001
Macroadenoma	87.3 %	71.6 %	0.014
Pre-existent diabetes	N = 8 10.1 %	N = 9 10.2 %	NS
Pre-existent HT	N = 13 16.5 %	N = 19 21.6 %	NS
Pre-existent CVE	N = 3 3.8 %	0	NS
Hypopituitarism at diagnosis	10.1 %	12.5 %	NS
Duration of follow up (months)	99 (88) (1–541)	78 (80) (3–376)	NS
Radiotherapy	N = 62 78.4 %	N = 21 23.9 %	<0.0001
Trans-sphenoidal surgery	N = 16 20.3 %	N = 72 81.8 %	<0.0001
Medical therapy	N = 51 64.5 %	N = 40 45.5 %	0.02
Control achieved	N = 33 43 %	N = 69 78.4 %	<0.0001
Duration to control (months)	40 (94.1) (1–482)	18 (72.8) (2–491)	<0.05
Cumulative GH exposure (GHy)	48.0 (55.4) (5.8–347.7)	16.5 (90.3) (1.5–758)	<0.001
Cumulative GH till control (GHy)	20.5 (32) (3.0–163.7)	9.8 (90.5) (2.0–757.3)	<0.001
Risk of new DM	N = 5 6.3 %	N = 3 3.4 %	NS
Risk of new HT	N = 13 16.5 %	N = 9 10.2 %	NS
Risk of new CVE	N = 23 29.1 %	N = 7 8.0 %	<0.001
Time to development of DM, HT or CVE (months)	23 (1–132)	65 (2–384)	0.013
Risk of hypopituitarism	N = 36 45.6 %	N = 25 28.4 %	0.037
Mortality	N = 28 30.4 %	N = 12 13.6 %	0.001

GHy, Growth hormone years; DM, diabetes; HT, Hypertension; CVE, cardiovascular events; NS, not significant

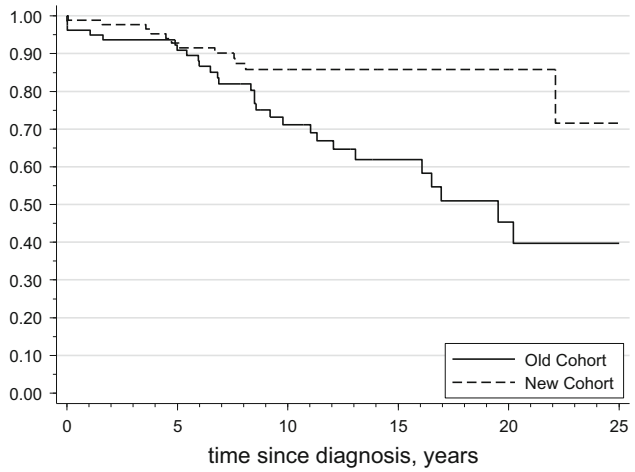

Fig. 1 Survival probability for 'old' and 'new' cohort separately—Kaplan–Meier Survival estimates

compared cohorts of patient between 1980–1994 and 1994–2010 and showed that the remission rates are as high as 70 % in later cohort with multi-modal treatment, but this study did not compare the mortality rates between the 2 cohorts [29].

The SMR for acromegaly in the 'New' cohort is equal to the general population though the overall SMR was 1.6 for the entire cohort. The Kaplan–Meier curves demonstrate a reduction in mortality over the follow up period on comparing the 'New' vs 'Old' cohort (Fig. 1). The incidence rates of comorbidities such as diabetes, hypertension and CVE were also much lower in the 'New' cohort and could have confounded to the improvement in mortality. This may be attributed directly to one or more of the following factors:

(1) The cure rates achieved were much better in the 'New' cohort and the duration to achieve the control was also significantly shorter (2) A significantly higher proportion of patients had surgery with no radiotherapy in the 'New' group, whereas the 'Old' group was largely treated with radiotherapy. Surgery would offer earlier remission and external beam radiotherapy may be associated with increased long term mortality [10] (3) The cumulative GHy exposure, overall was lower in the 'New' group, which could have direct implication for development of vascular morbidity (4) The cumulative GHy exposure until the point of control of disease was also much lower in the 'New' cohort thereby reducing the disease burden. Calculating this parameter is useful to balance out the longer duration of follow up with normal annual random GH levels in many patients of the 'New' cohort (5) New incidence of

Table 4 Standardized mortality ratios for all cause death from external analysis

Cohort	Observed	Expected	SMR (95 % CI)	*P*
'Old' (up to 1992)	28	11.4	2.5 (1.7–3.6)	<0.001
'New' (since 1992)	12	12	1.0 (0.6–1.8)	NS
Total	40	23.4	1.6 (1.3–2.3)	<0.001

NS, not significant

Table 5 Comparison between patients who died vs survivors in 'old' cohort

	Died Median (Range)	Survivors Median (Range)	*P*
N	28	51	
GH at diagnosis (mcg/L)	14.2 (3.2–200.0)	7.7 (0.7–64.3)	NS
Cumulative GH (GHy)	51.5 (7.6–211.7)	34.5 (5.8–347.7)	NS
Cumulative GH till control (GHy)	17.0 (4.3–163.7)	22.1 (3–83.3)	NS
Occurrence new DM, HT or CVE	21/28	2/51	<0.0001
Time to develop new DM, HT or CVE (months)	34 (1–88)	71 (68–74)	0.08
Radiotherapy	19/28	43/51	NS
Control achieved	6/28	27/51	0.009
Duration to cure (months)	70 (11–482)	37 (1–221)	NS

GHy, Growth hormone years; DM, diabetes; HT, Hypertension; CVE, cardiovascular events; NS, not significant

Table 6 Comparison between patients who died vs survivors in 'new' cohort

	Died Median (Range)	Survivors Median (Range)	*P*
N	12	76	
GH at diagnosis (mcg/L)	5.4 (1–81.0)	7.8 (0.7–130.0)	NS
Last GH (mcg/L)	0.3 (0–120.0)	1.2 (0.0–70.0)	NS
Cumulative GH (GHy)	5.3 (1.5–29.2)	16.8 (0.6–758.0)	0.04
Cumulative GH till control (GHy)	3.5 (1.6–28.9)	11.5 (1.7–757.3)	NS
Occurrence of new DM, HT or CVE	3/12	13/76	NS
Time to develop new DM, HT or CVE (months)	102 (17–256)	110 (2–384)	NS
Radiotherapy	3/12	19/76	NS
Control achieved	9/12	60/76	NS
Duration to cure (months)	13 (5–176)	19.4 (2–491)	NS

GHy, Growth hormone years; DM, diabetes; HT, Hypertension; CVE, cardiovascular events; NS, not significant

cardiovascular risk factors and events could contribute to mortality significantly, as these are the major cause of death in acromegaly [2]. These were lower in the 'New' cohort.

There have not been many studies that have looked at predictors for development of comorbidities but one recent study showed that pre-treatment IGF-1 as being a good predictor [29]. Our study reports that 34 % of patients developed new metabolic or vascular events during follow up. The overall cumulative GHy as well as the GHy until control was achieved, was high in this cohort in comparison to those who did not develop these events. Our mortality data also showed that the time to developing these events were significantly lower in those who died (45 vs 154 months, $p < 0.01$; Table 1). This confounded with the fact that the patients who died had higher cumulative GHy could suggest cumulative GHy as a predictor of vascular events. These substantiate the fact that reducing the cumulative GHy, either by curing early (thereby reducing the duration of exposure) or by controlling better (thereby reducing the absolute GH values) could significantly reduce the vascular morbidity burden that is the predominant cause of death in acromegaly. As the duration and severity of GH exposure is related to mortality and the results of our study showing improvement in mortality with better and earlier remission rates, it is crucial that patients with acromegaly are treated early and aggressively.

Measurement of cumulative exposure to GH is suggested as a novel parameter to quantify GH exposure over time and is a more accurate reflection of severity and burden of the disease. Sherlock et al. [21] have published recently on the limitations of using the traditional 'last available GH' and the lower mortality rates with lower levels of 'time-dependant' growth hormone measurements. Jayasena et al. [30] recently published a study looking at IGF-1 indices as a marker of disease burden and showed this to be associated with increased morbidity in acromegaly. We used cumulative GHy as a marker to provide a numerical representation of the disease burden and our study provides further positive evidence for the importance of using GHy, rather than GH at diagnosis or at last clinic visit, to predict risk of mortality and morbidity. Numerous years are in general lost before the actual diagnosis of acromegaly is made; similarly patient compliance in adhering to medical treatment and followup after definitive treatment could be a challenge—both of these issues add up further to the cumulative GHy [31, 32]. Sherlock et al. [21] had used an adjustment during calculation of time-dependant GH measurement, to make up of the years lost. We did not do it as part of our study to keep this measurement more practice and reproducible in clinical practice.

The prevalence rates of comorbidities such as diabetes and hypertension are lower in comparison to other published epidemiological studies [22, 29]. This difference could be attributed to two factors: firstly, the data on these conditions were based on clinical prevalence based on documentation rather than analysis of diagnostic test and secondly, the diagnostic criteria for these comorbidities have changed several times over the course of the duration of this study. The data on the 'old' cohort was truncated to all available

parameters till the year 1992, to facilitate comparison with the previous published paper from Bates et al. [13].

Predictors of mortality in acromegaly have a long been a debated issue. Hypopituitarism and radiotherapy have been consistently shown to be associated with increased mortality [10, 21] whereas GH at diagnosis or the latest GH or IGF-1 has provided conflicting evidence [11, 16, 17]. As previously shown, conventional radiotherapy was associated with higher mortality in our study; and achieving control of the disease was associated with lower mortality. The use of medical therapy was not different between the two groups (55.2 vs 54 %, p = NS). The cumulative GH exposure as a predictor for mortality did not reach statistical significance in this analysis though it was significantly higher in patients who had died. It appears that achieving control of the disease is more important for reducing mortality; however normalization or reduction of GH levels is important to reduce the vascular comorbidities associated with the condition which would significantly contribute to reduced quality of life and to mortality.

This is the first study that provides an evidence to prove that there has indeed been an improvement in mortality and morbidity associated with acromegaly over 50 years, by reporting on two similar cohorts during the first and second 25 years of management at a single centre. This study clearly demonstrates that there has been a significant improvement in mortality (30.4 vs 13.6 %, $p = 0.001$) over the decades, largely driven by better cure rates and lower GH exposure from acromegaly. The time to achieve control of disease (33 vs 69 months, $p < 0.0001$) and cumulative GHy (48.0 vs 16.5, $p < 0.001$) were significantly higher in the 'Old' cohort. This was further confounded by the lower number of patients treated with surgery and the higher use of radiotherapy. The risk of developing new diabetes or hypertension was similar; however the risk of CVE was significantly high in the 'old' cohort (29.1 vs 8.0 %, $p < 0.001$). This study is in keeping with recent publications showing that better access to surgical treatment and expertise in managing acromegaly with multiple modalities of treatment, is associated with better cure rates [29, 33]. Though it could be argued that this is a single centre study and concurs with what is obvious in daily practice, it provides documented evidence of this improvement and further relates the importance of cumulative GH (and not the latest GH) as a possible predictor of mortality. The sub-analysis done, comparing the died vs survivors in the two cohorts (Tables 5, 6) showed important differences that have evolved with time: the incidence of new metabolic and vascular events were higher and happening earlier in the 'old' cohort with lesser proportion achieving control, the cumulative GHy being comparable. The GHy of the 'old' cohort was higher than the 'new' cohort in general thereby clearly proving the impact of the disease burden.

There are some limitations to our study. Firstly, the total number of patients in some of the analyses was small, which therefore may not provide adequate statistical power for the analysis and may therefore be a reason for lack of statistical significance. Secondly, the data on cause of deaths is lacking and risk of development of new cancers not recorded, and therefore this could not be part of this publication. Thirdly, cumulative GH has been calculated as mean of values of GH over successive years to provide an approximation of GH exposure for a particular calendar year and certain treatment such as surgery may reduce the GH values rapidly making statistical adjustment to accommodate this difficult. Similarly, the duration of acromegaly that may precede the actual diagnosis and the inherent risk of GH exposure during that period cannot be calculated but equally could be an inherent biasing factor in development of complications and mortality. Fourthly, for the sub-analysis performed comparing 'new' with 'old', we only used all relevant data on the 'old' cohort until 1993 and deliberately excluded clinical data further on, to provide an equitable comparator. The year 1993 has been purely arbitrarily chosen as a cut off point, entirely because of the previous publication from our own centre. We also acknowledge that many assays, diagnostic criteria and monitoring methods have changed over the decades; also, the cumulative GH of 'older' cohort could be lower if readjusted based on the more sensitive newer assays. Statistical adjustments to make up for these variations in practice are practically not feasible. However, this is the first study that provides an internal comparison between similar sized cohorts of patients with acromegaly, from a single centre and treated by a limited number of specialist endocrinologist with a long duration of follow up, which reiterates the improvements achieved in morbidity and mortality associated with acromegaly. The purpose of the study is therefore to highlight the importance of achieving control of GH levels early, to minimise the exposure of various tissues to supra-physiological doses of GH and thereby reduce mortality and morbidity. Though clinical monitoring of treatment and control of acromegaly would be based on GH and IGF-1 levels, a combination of the magnitude of GH levels and the duration of acromegaly should prompt the clinician about the increased risk of morbidity and mortality.

Conclusion

This internal single centre comparison study clearly demonstrates that significant improvement in mortality and cardiovascular morbidity has been achieved in the

management of acromegaly over the past five decades. GH exposure, as measured by cumulative GH, appears to be linked to mortality and cardiovascular morbidity. Our study also provides supporting evidence that early and 'curative' treatment of acromegaly would provide mortality benefit and possible reduction in cardiovascular morbidity burden. It is therefore imperative that aggressive treatment options are used to achieve remission in acromegaly to prolong complication-free life expectancy.

Compliance with ethical standards

Conflicts of interest Nothing to declare.

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