

Mortality in Cushing's Disease

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Key Words

Cushing's disease · Mortality outcomes · Determinants of mortality

Abstract

The causes of premature death in untreated Cushing's syndrome are vascular disease (myocardial infarction/stroke), uncontrolled diabetes mellitus and complications and infections. Long-term mortality outcome studies on pituitary-dependent Cushing's disease (CD) are limited to six studies in the English language literature. This paper reviews these studies on CD, other causes of Cushing's syndrome being excluded, because CD represents 80% of patients with the syndrome. The period covered by these studies (1970–1990) is when transsphenoidal surgery was well established as primary treatment for CD. Two studies were exclusively from surgical centres and are likely biased in favour of surgically resectable adenomas, so this needs to be borne in mind when interpreting their results. The criteria for remission of hypercortisolism and persistent disease were variable. The overall number of patients in each report is small, and the number of deaths even smaller by epidemiological standards giving very wide confidence intervals to the standardised mortality ratios (SMR). Moreover, follow-up time was relatively short (median 10–12 years) for a disease diagnosed in the patients' late 30s. Notwithstanding the above limitations of retrospective studies, and potential for posi-

tive bias, the overall SMR of around 1.5 was not significantly different from the relevant normal population for those patients deemed in remission. However, SMR was significantly worse for those patients with persistent disease. Where it was possible to analyse contributing factors to mortality, the presence of hypertension and diabetes mellitus, in addition to persistence of hypercortisolism, was shown to be significant. It remains possible that an overall SMR in 'cured' patients would be significant given a larger cohort, followed for longer, and with more deaths. What is clearly required is a multicentre prospective cohort study with >30 years' follow-up to answer the question definitively and identify the contributing factors in detail in order to achieve optimum long-term outcome.

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Introduction

Cushing's syndrome is a rare condition, with an estimated prevalence of 2–3/million population/year [1], although this might be higher in selected populations such as poorly controlled diabetics, young osteoporotic women and men, and young hypertensives [2]. Further, mild (subclinical) Cushing's syndrome may be detected in patients with incidentally discovered adrenal adenomas on abdominal CT scan performed for other reasons. Untreated Cushing's disease (CD) is associated with a very

Table 1. Mortality in CD

	Period covered	Patients (mean age at treatment)	Remission of hypercortisolism	Follow-up duration, months ¹	Deaths	Overall SMR (95% CI)	p
Etxabe et al. [7]	1975–1992	49 (39)	36/41 (87%)	56 (6–210)	5/49 ²	3.8 (2.5–17.9)	<0.05
Swearingen et al. [8]	1978–1996	161 (38)	137/161 (85%)	96 (12–240)	6/159 ³	0.98 (0.44–2.2)	NS
Pikkarainen et al. [10]	1981–1994	63 (44)	20/20 (100%) ⁴ 25/43 (58%) ⁵	84 (0–180)	2/20 6/43	1.35 (0.16–4.89) 2.67 (0.89–5.25)	NS NS
Lindholm et al. [1]	1985–1995	73 (41) ⁶ 26 (51) ⁷	56/73 (77%) not stated	96 (36–168) 96 (36–168)	7/73 11/26	1.7 (0.7–3.5) 11.5 (5.7–20)	NS <0.001
Hammer et al. [9]	1975–1998	289 (37)	236/289 (83%)	132 (6–288)	17/236 ⁸ 25/285 7/53	1.18 (no CI) ⁹ 2.8 (no CI) ¹⁰	NS ?Sig.
Dekkers et al. [11]	1977–2005	74 (39)	59/74 (80%)	120 (36–204)	12/74	2.39 (1.2–3.9) 1.8 (0.71–3.37) ¹¹ 4.38 (1.38–9.07) ¹²	<0.05 NS <0.05

¹ Median (range); ² no information on 8 patients; ³ two patients uncontactable; ⁴ adrenal adenoma; ⁵ CD; ⁶ proven CD at histology, ⁷ unproven CD – clinically/biochemically ACTH-dependent hypercortisolism; ⁸ four deaths in first 3/12 post-operatively – excluded as perioperative; ⁹ initial remission; ¹⁰ initial persistent disease; ¹¹ remission after initial surgery; ¹² persistent disease after initial surgery.

poor prognosis, estimated 5 years' survival of 50% [3], though this is dramatically improved to 86% after bilateral adrenalectomy [4].

The main causes of the poor outcome in untreated patients are vascular disease, (strokes, myocardial infarction), uncontrolled diabetes mellitus and infections. Long-term outcome studies in patients with Cushing's syndrome are very limited. In contrast to patients with acromegaly and non-functioning tumours where there are now extensive data on factors which determine mortality, no such data are available for Cushing's syndrome. For example, we know that in acromegaly the duration of disease before diagnosis is a predictor for mortality as is age at diagnosis and the presence of hypertension or cardiac disease at diagnosis [5]. It is not known whether similar variables predict mortality in CD, though intuitively this would seem likely. Further, we know that a specific biochemical target with respect to GH and IGF-1 is predictive of mortality in acromegaly [6]. Is there such a relationship for plasma cortisol in Cushing's syndrome? The question is whether elimination of hypercortisolism, even if present for several years before treatment as is often the case, can restore mortality rates to that of the reference population. The purpose of this brief review is to examine what data are available and define criteria for optimal long-term survival.

Methods

Since 80% of Cushing's syndrome is caused by ACTH-secreting pituitary adenomas (CD), this review is restricted to those reports where CD can be distinguished from subgroups with ectopic ACTH syndrome and primary adrenal pathologies. A search of PubMed using the terms Cushing's syndrome and long-term outcomes/results and mortality yielded six reports between 1994–2007. It was surprising to find that many centres with an international reputation which have published extensively on the diagnosis and management of Cushing's syndrome have not reported on mortality outcomes despite having treated many patients over many years. There are limitations to extrapolating from the six published papers since data are not reported uniformly, making comparisons between them difficult. This review concentrates on (long-term) mortality (excluding that deemed to be immediately post-operative) and the causes of death. It does not discuss surgical remission rates per se, only if relevant to mortality.

Results

A summary of the results pertaining to mortality (table 1) and predictors of it (table 2) is presented. Some general comments are pertinent. The period covered from mid-1970s to late 1990s spans the time when transsphenoidal surgery for pituitary adenomas was well established. The numbers of patients are small by epidemiological standards, the number of deaths even smaller

Table 2. Independent predictors of mortality in CD

	Predictors of increased mortality	Comment
Etxabe et al. [7]	older age at diagnosis, persistent hypertension; abnormalities of CHO metabolism	
Pikkarainen et al. [10]	no information	
Swearingen et al. [8]	older age at diagnosis	no information on HT or DM
Lindholm et al. [1]	persistent hypercortisolism after initial surgery	No information on HT or DM
Hammer et al. [9]	persistent hypercortisolism after initial surgery (but only after 10 years' follow-up)	No information on HT or DM
Dekkers et al. [11]	persistent hypercortisolism after initial surgery	No information on HT or DM

HT = Hypertension; DM = diabetes mellitus.

amounting to less than 10% of the total patient population. Therefore, information on causes of death is limited and cannot be statistically analysed reliably. The mean age of treatment (late 30s) is similar across all reports and the median follow-up duration (about 10 years) is similar, except for the report by Etxabe and Vazquez [7]. This means that the age of the patients at the end of the study is <60 years, so unsurprisingly the number of deaths is small given the improvements in the health of the population over this 30-year period. Only the first and smallest study by Etxabe and Vazquez [7] reports on the relationship of hypertension and carbohydrate metabolism to mortality. Some of the other studies reported primarily by pituitary surgeons [8, 9] are somewhat biased as they will include only those 'offered' to them by endocrinologists/physicians and are likely biased in favour of patients thought by the latter to do well from surgery. This may explain the very high initial remission rates in the surgical series compared to the others. The criteria for remission/surgical failure/recurrence are fairly consistent across all the studies and are based on resolution of clinical symptoms/appearances, urine free cortisol normalisation and plasma cortisol after overnight dexamethasone suppression testing. In regard to the latter, one series [9] uses <140 nM as the criteria for remission after overnight dexamethasone, which would be regarded by most

today as not sufficiently stringent. It is appropriate to comment on each individual study in turn since each brings out interesting points and has its own caveats to their conclusions.

Etxabe and Vazquez (1994) [7]

The smallest study by far; no information provided about 8/49 patients reducing the effective total number to 41. Treatments were variable with 18 patients undergoing bilateral adrenalectomy, inferred as primary treatment, 16 patients had pituitary radiotherapy. The standardised mortality ratio (SMR; 3.8) showed significant increase despite 87% of patients achieving remission, but the confidence interval is wide and it is based on only five deaths. It is not clear how long after initial/subsequent treatments patients were defined as being in remission. The authors comment that the SMR for vascular disease (5, CI 3.4–48.6) was significant but this is based on only three deaths, so must be regarded with caution. This was the only report to enter hypertension and disordered carbohydrate metabolism into a multivariate analysis of predictors of mortality. Perhaps unsurprisingly older age at diagnosis, when the impact of co-morbidities with hypercortisolism might be expected to be greater, was a predictor of mortality.

Pikkarainen et al. (1999) [10]

This single-centre study from Helsinki reports mortality in all cases of Cushing's syndrome, including ACTH-dependent CD (n = 43), and ACTH-independent Cushing's syndrome including adrenal adenomas (n = 20) combined and separately. There is no specification on the biochemical criteria used to make the diagnosis, nor what criteria define remission after hypophysectomy in CD. It is unclear how many CD patients were in remission after hypophysectomy and at what time after the operation. Mortality data are reported separately for adrenal adenoma and CD (table 1), and the 95% confidence interval is wide, reflecting the small number of deaths (n = 6 for CD). The age of death for CD patients ranged from 61 to 80 and 3/6 died from cardiovascular causes, which proportion is said to be no different from the general Finnish population, though no statistics are available. Overall, this study is lacking in detail and numbers of patients and deaths are small. No predictors of mortality are identified. Notwithstanding this, the conclusion is that adequate treatment of CD seems to confer a normal mortality rate.

Swearingen et al. (1999) [8]

The main concern with this large series of 161 patients is that only those who had transsphenoidal surgery were

included so there are no data on those Cushing's patients who were considered unfit for surgery or treated by other modalities. Further, 90% of the patients had microadenomas; only 17 patients had macroadenomas; therefore, the mortality outcomes (only 6 deaths in total over a median follow-up of 8 years) reflect that of a highly selected group of patients that would be expected to have the best surgical outcomes with respect to restoring eucortisolaemia. Indeed, 10 year 'cure' rates were 91% for 125 microadenomas versus 55% for 11 macroadenomas. It is unclear why the 11 macroadenomas remained 'uncured' at 10 years when it is reported that the majority of surgical failures underwent bilateral adrenalectomy.

Lindholm et al. (2001) [1]

The 'power' of this study was the ability of the Danish National Patient Register to identify all patients with Cushing's syndrome in Denmark over their recruitment period (1985–1995), so it is a truly unbiased cohort of patients. Further, the numbers and data were such that the authors were able to categorise the patients accurately into those with Cushing's syndrome caused by CD, adrenal tumours and cancer associated (either malignant or carcinoid). Consequently, it was possible to compare mortality outcomes between the subgroups. Moreover, within the CD cohort, a subgroup was identified as 'aetiology unproven' in whom a pituitary aetiology was inferred but in whom histology was inconclusive or no tissue was available. This subgroup was also 10 years older at diagnosis. This subgroup had a particularly poor outcome (table 1) in comparison to those in whom a pituitary cause was confirmed histologically. This latter subgroup (the largest) had a good 'cure' rate of hypercortisolaemia and a normal long-term mortality rate. Unfortunately, it is not possible to work out the 'cure' rate in the 'aetiology unproven' subgroup. The other interesting observation from this study was that the mortality in patients with unilateral adrenal adenoma (4/37) was not significantly different from that of the normal population (SMR 3.48, CI 0.95–8.9). The only adverse predictor of mortality identified was persistent hypercortisolism after initial surgery.

Hammer et al. (2004) [9]

In the largest series by far (n = 289), all patients underwent transsphenoidal hypophysectomy as initial treatment by a single surgeon for presumed CD; 253/289 (87.5%) cases were confirmed by histology as ACTH adenoma or corticotrope hyperplasia. As with the other surgical series [8], the outcomes apply to a somewhat select-

ed population of patients, and the same caveats apply to the conclusions; the main one being that selection for pituitary surgery was presumably made by numerous clinicians by unstated and varying criteria. Initial cure rate was defined in the first week after surgery, but also accepted if the cortisol levels fell to normal within the first 6 months after surgery; the rate was high, although the criterion of suppression of plasma cortisol to <140 nM would not be considered stringent enough by 2009 criteria. Excluding 4 patients who died within the first 6 months after surgery, 25/285 patients died during follow-up. When compared to the normal population, a greater proportion of patients in the initial persistent disease subgroup (p < 0.01) had died compared to the initial remission subgroup (p < 0.28), although no confidence intervals are provided. Interestingly, the Kaplan-Meier analysis shows that the decreased survival of the initially persistent disease cohort is only apparent after 10 years. The median age at death of those in the initially persistent disease cohort (n = 7) was 61 versus 71.7 years for the initial remission cohort (n = 17; no statistical analysis of significance provided), although the median duration of survival after surgery in those that died was similar (13.7 vs. 12.7) for those patients with initially persistent disease (n = 53). Long-term follow-up data are only available on just over half (28/53) of the patients, and the final status was persistent disease despite further treatments in 10/28 patients. If it is assumed that a similar proportion of the 25 patients for whom no data are available still have persistent disease, then 36% (19/53) never had their hypercortisolaemia adequately treated. Of the initial remission group (n = 150) for whom long-term data could be obtained, 137 were still in remission, i.e. 13 (9%) recurrences at a median interval of 5 years. If the same recurrence rate is assumed for the remaining 86 patients for whom data are not available, an overall disease-free long-term remission rate is 91% for the initial remission cohort versus only 64% for the initial persistent disease cohort. These data would suggest that long-term persistent hypercortisolaemia is the determinant of poorer outcome, and correction of this as soon as possible is paramount.

Dekkers et al. (2007) [11]

Although this is another surgical series from a single centre in Leiden, it is of particular interest because it compares mortality outcomes in patients with CD with that of non-functioning pituitary tumour patients, thereby inferring that any increase in mortality in CD would be due to hypercortisolaemia per se rather than hypopituitarism/pituitary tumour in general. Somewhat sur-

prisingly, compared to the literature, the non-functioning pituitary tumour cohort (n = 174) did not have an increased SMR (1.24; CI 0.85–1.74) compared to the normal population, e.g. Tomlinson et al. [14]. The whole CD cohort had an increased mortality despite 93% being in long-term remission (table 1). However, the SMR in CD with remission after initial surgery was not significantly different from normal at 1.8 (CI 0.71–3.37) versus SMR of 4.38 (1.38–9.07) for those with persistent disease; although the numbers of deaths in each subgroup are not stated, they must have been small as the total cohort only had 12 deaths. Despite the fact that many of those with initial persistent or recurrent disease must have been cured of their hypercortisolaemia as the long-term ‘cure’ rate was 93%, these still had a worse outcome. We are not told, and it is not possible to ascertain from the report, but perhaps the majority of deaths were in the long-term persistent disease subgroup (7% of total = 5 patients).

Conclusions

Despite the fact that the six series reviewed included relatively small numbers of patients by epidemiological criteria and an even smaller number of deaths, some common conclusions emerge:

(1) The most important is that long-term mortality outcomes for successfully treated CD, that is restoration of eucortisolaemia, are not different from those of the general population over a 10- to 20-year follow-up period. However, a word of warning; these patients were on average about 40 years of age at diagnosis, and many would not have reached 60 years of age at study end. Further, two studies [7, 8] identified older age at diagnosis as an independent predictor of death. So it is important to continue to follow up these cohorts ultra-long term (>30 years) to confirm that ‘cured’ CD is compatible with normal longevity (as for example appears to be the case with ‘cured’ acromegaly). However, it remains possible that SMRs of >1.5 may be significant in longer studies with larger numbers of deaths (cf. acromegaly papers).

(2) The studies that have related surgical outcome with respect to initial remission of hypercortisolaemia to mortality show that if this is achieved, mortality rate is not increased even though that of the overall cohort may be increased. It is the subgroup of patients with persistent disease that have the worst outcome. Despite the well-recognised fact that hypercortisolaemia may have been present for months or years before effective treatment, it is still possible to ‘normalise’ mortality. In none of the

Table 3. Definition of initial remission of CD

	Criteria	Time
Etxabe [7]	return of UFC to normal ¹ and normal cortisol suppression with dexamethasone ¹	not stated
Pikkarainen [10]	normal UFC, disappearance of symptoms and no relapse	not stated
Swearingen [8]	fasting serum cortisol <138 nM (5 µg/l) and UFC <55 nmol/day (<2 µg/day)	within 10 days of surgery
Lindholm [1]	subnormal plasma cortisol 30 min after synacthen (<500 nM or 18 µg/l) and/or UFC <50 nmol/day (<2 µg/day); UFC <250 nmol/day (9 µg/day) >5 years postoperatively	12–180 days after surgery
Hammer [9]	basal or dexamethasone-suppressed plasma cortisol <140 nM (5 µg/l) or if above unavailable low or normal plasma or UFC and resolution of clinical features and no additional treatment	within 1st week after surgery within first 6 months after surgery
Dekkers [11]	plasma cortisol <100 nM (3.5 µg/l) after O/N dexamethasone and normal UFC [<220 nmol/day (8 µg/day)] × 2	3–6 months after surgery

UFC = Urinary free cortisol.

¹ UFC; to convert nmol to µg divide by 28.

studies is any attempt made to relate duration of disease before treatment to worse outcome as has been shown in acromegaly [5].

(3) The above conclusions should be restricted to the largest cohort of patients that have a proven (histologically) ACTH-secreting pituitary adenoma as the cause of their Cushing’s syndrome, i.e. CD. This is exemplified in the Danish study [1] wherein the subgroup with ‘unproven’ CD had a poorer outcome.

(4) It follows that it is paramount to correct the hypercortisolaemia as quickly as possible to reverse increased mortality. In the majority of cases (70–90%), this can be achieved by transsphenoidal pituitary surgery, but this must be performed by experienced pituitary surgeon using the latest techniques. Failure of initial surgery or recurrence must be dealt with promptly and effectively. Notwithstanding the 20–30% risk of developing Nelson’s

syndrome, the one sure way to do this is by laparoscopic bilateral adrenalectomy. It would be especially interesting to know the long-term outcome of a subgroup of failed hypophysectomy plus bilateral adrenalectomy in whom by definition their hypercortisolism will be 'cured'.

Clearly, since the optimum outcomes are in those patients who achieve initial remission, it is critical to examine the criteria used to define remission in these studies. These are shown in table 3, and it is immediately apparent that these differ. Moreover, all quote either plasma cortisol or urinary free cortisol values, and the 'normal' ranges will have varied over the duration of the studies and the assays used for measurement. In other words, there is lack of standardisation. What is not clearly apparent from the reports is the clinical 'cure' rate. Admittedly, this is difficult to define but some indication of resolution of the cardiovascular risk factors would have been useful, e.g. what proportion of patients who were hypertensive or di-

abetic before treatment were able to come off medication afterwards. Another issue to be considered is that according to some reports [12, 13] some cardiovascular risk factors persist even after apparent 'cure' of hypercortisolism. If that is so then why is the mortality normalised? It would imply that the persistence of these risk factors is not particularly relevant or has relatively minor impact, unless of course the duration of follow-up is too short for these to impact on mortality.

In short, CD is bad for you physically, emotionally, and for your survival. The good news is that early effective treatment not only cures your symptoms but appears to normalise your survival chances.

Disclosure Statement

The author has no financial disclosures to declare.

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