Mortality of patients with Cushing's disease

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Abstract

Cushing's disease is a rare condition of cortisol excess attributed to a pituitary adenoma with an annual incidence of 1.2-2.4 cases per million population. It is associated with several co-morbidities leading to increased mortality predominantly due to cardiovascular disease. Despite the advances in its diagnosis and management, survival can be compromised even after apparent successful treatment. Minimizing the duration and extent of exposure to hypercortisolaemia by early diagnosis and rapid, effective therapeutic interventions, as well as close monitoring and aggressive control of cardiovascular risk factors are vital for improving outcomes of the patients.

Introduction

Cushing's disease (CD) is a rare condition of cortisol excess attributed to a pituitary adenoma. Epidemiological studies suggest an annual incidence of 1.2-2.4 cases per million population [1, 2, 3, 4, 5, 6, 7] and a prevalence of 12-79 cases per 100,000 [1, 4, 6, 8, 9, 10]. Median age at diagnosis is 40 years (range 10-76) [11, 12] with a clear female preponderance (73-93% of the patients in published series are women) [4, 11, 13, 14, 15, 16, 17, 18, 19, 20].

Cortisol excess is associated with several co-morbidities (central obesity, insulin resistance, abnormalities in glucose metabolism, hypertension, dyslipidaemia, hypercoagulability, immunosuppression, myopathy, osteoporosis and neuropsychiatric disturbances, such as cognitive impairment and depression) [21, 22, 23]. These do not only have an impact on the quality of life [24] but also lead to a dramatic reduction in the survival of the patients [1, 3, 4, 11, 12, 13, 14, 15, 17, 19, 20, 25, 26, 27, 28].

Herein, we review the published literature on the mortality of patients with CD and factors affecting it.

Mortality in CD

A summary of the studies reporting on standardized mortality ratios (SMRs) discussed in this review is shown in Table 1. The majority of these studies confirms that patients with CD have mortality higher than that of the general population [1, 4, 11, 12, 13, 14, 15, 19, 20, 28].

Etxabe *et al.* [1] reported on 49 patients diagnosed with CD between 1975 and 1992 and followed-up for a median period of 56 months. Remission of the CD after various therapeutic approaches [defined as normalization of 24hr urinary free cortisol (UFC) and recovery of cortisol suppressibility following dexamethasone administration] was achieved in 87.5% (36/41) of the patients. No recurrence was detected during a mean observation interval of 27 months from the date of transsphenoidal surgery (TSA). Mortality was almost 4 times higher than expected (SMR 3.8, 95% CI 2.5-17.9) and was significantly elevated in women (SMR 4.5, 95% CI 2.94-21). Vascular disease was the most frequent cause of death. On multivariate analysis, persistence of hypertension and abnormalities in glucose metabolism were independent predictors of mortality.

Swearingen *et al.* [28] studied 161 patients who underwent TSA for CD between 1978 and 1996. The majority had microadenomas (89%) and remission during the first 10 post-operative days (defined as fasting serum cortisol <138 nmol/L and UFC <55 nmol/24hours) was observed in 85% of them. Data on remission at last follow-up were not provided but during a median observation period of 8 years, 7% of the cases were diagnosed with

recurrence of the CD. Multiple treatments were offered to 29 patients. In this series, survival was not different to that of an age- and sex-matched sample from the USA population (SMR 0.98%, 95% CI 0.44-2.2). A potential drawback of this study is that it may represent a well selected group of patients who were most likely to have optimal surgical results, thereby affecting mortality outcomes.

Dekkers *et al.* [15] assessed mortality in a series of 74 patients (85% with microadenoma) managed by TSA between 1977 and 2005. Biochemical cure was defined as suppression of serum cortisol <100 nmol/L on the overnight dexamethasone suppression test and normal UFC levels on two consecutive samples. Median follow-up was 10 years and long-term remission of the CD was achieved in 93% of the patients. Mortality was increased in the total group (SMR 2.39, 95% CI, 1.22–3.9), as well as in those with persistent disease (SMR 4.38, 95% CI, 1.38-9.07). This was not the case for patients in remission after initial surgery (SMR 1.80, 95% CI, 0.71–3.37). Notably, 42% of the deaths were attributed to vascular causes.

Clayton *et al.* [13] studied 60 patients with CD diagnosed between 1958 and 2009. The biochemical criteria for defining remission of the Cushing's included urinary steroid excretion within the normal limits, blood cortisol <100nmol/l on overnight dexamethasone suppression test or average plasma cortisol <350 nmol/l during a cortisol day curve for patients on metyrapone or bilateral adrenalectomy within three years from first treatment. Failure to achieve these targets despite several treatment modalities within three years was defined as persistence of disease. At the end of a median follow up period of 15 years, 90% of the patients were considered to be in remission. Mortality was increased in all groups (SMR total group 4.8, 95% CI 2.8-8.3, group in remission 3.3, 95% CI 1.7-6.7, group with persistent disease 16.0, 95% CI 6.7-38.4). Vascular causes were responsible for 9/13 deaths (SMR 13.8, 95% CI 7.2-26.5) and presence of diabetes mellitus and hypertension had a negative impact on survival. This series covers an extensive period during which significant advances in the diagnosis and management of Cushing's took place and this needs to be taken into account when interpreting the results.

Bolland *et al.* [4] reviewed 188 patients with CD diagnosed between 1960 and 2005 in a nationwide study (30 macroadenomas and 158 microadenomas). Biochemical cure was considered if at last follow-up the patients had adrenal insufficiency and required glucocorticoid replacement or were not on glucocorticoids and had normal UFC or, in the setting of a possible relapse, had adequate cortisol response on the overnight dexamethasone suppression test. At last follow-up, 93% of the cases with macroadenoma (median observation period 7.8 years) and 91% of those with microadenoma (median observation period 7.6 years) were cured. SMR was elevated in both microadenoma (SMR 3.2, 95% CI 2.0-4.8) and macroadenoma (SMR 3.5, 95% CI 1.3-7.8) patients. Notably, mortality was

increased even in patients with microadenoma cured after first surgery (SMR 3.1, 95% CI 1.8-4.9), whereas no difference was found in the survival between those diagnosed before or after 1980.

Hassan-Smith *et al.* [12] reviewed a series of 80 patients who underwent TSA between 1988 and 2009. Initial remission was defined as a morning post-operative cortisol value of ≤1.8 μg/dl (measured between day 4 and week 6), and cure as absence of hypercortisolism at last follow-up. During a median observation period of 10.9 years, mortality was found increased in the total group (SMR 3.17, 95% CI 1.70–5.43). SMR for those cured at last follow-up was 2.47 (95% CI 0.80-5.77) and for those with persistent/recurrent disease at last follow-up was 4.12 (95% CI 1.12-10.54).

Ntali *et al.* [11] reviewed 182 subjects with CD followed up for a median period of 12 years. Remission of hypercortisolaemia was defined as an undetectable 9.00 am serum cortisol (based on local assays) after surgery. Remission after pituitary radiotherapy was considered if the patient had achieved normal UFC or a mean serum cortisol between 150 and 300 nmol/L on a 5-point cortisol day curve. At last assessment, 85% of the patients were in remission after various management approaches. Overall, mortality was significantly elevated (SMR 9.3, 95% CI 6.2–13.4) with the majority of deaths attributed to cardiovascular causes or infections. In this series, survival was also significantly reduced in the subgroup of patients remaining on long-term remission after their initial surgery (SMR 10.8, 95% CI 6.0-18.0).

Yaneva *et al.* [20] reported on 240 patients with CD managed with various treatment modalities between 1965 and 2010 and followed-up for a median period of 8.8 years. Cure of the Cushing's was defined as absence of cortisol excess (normal/low UFC or 17-OH and ketosteroids in the earlier period and adequate response of cortisol on the overnight dexamethasone suppression test) to the time of the last clinic visit. Amongst the patients treated by TSA alone or in combination with other approaches, 79% were characterized as cured at last assessment. SMR was found similar to that of the general population (1.88, 95% CI 0.69-4.08**).**

Ragnarsson *et al.* [19] reported on 502 patients with CD diagnosed between 1987 and 2013 in a nationwide study. The assessment of the remission status was based on information about resolution of clinical features of the Cushing's, UFC, midnight salivary or serum cortisol, cortisol suppression on dexamethasone suppression test, adrenal insufficiency and/or bilateral adrenalectomy and was confirmed in 83% of the patients. Median follow-up was 13 years. Mortality was increased in the total group of patients (SMR 2.5, 95% CI 2.1-2.9) but also in those in remission (SMR 1.9, 95% CI 1.5-2.3) or not (SMR 6.9, 95% CI 4.3-10.4). Excess mortality was associated with cardio/cerebrovascular disease and infections. Notably, SMR due to cardiovascular diseases was increased in both remission and non-remission groups.

Finally, a multicentre, multinational, retrospective cohort study using individual case records from specialist referral centres in the UK, Denmark, the Netherlands, and New Zealand by Clayton *et al.* [14] investigated the mortality of patients in remission for a minimum of 10 years at study entry and no subsequent relapse until the database was frozen or until the death. Median follow-up from the time point entering the study was 11.8 years. Interestingly, SMR was found high in this patient group (SMR 1.61, 95% CI 1.23–2.12) with a 61% increase in the mortality risk. SMR for circulatory disease was 2.72 (95% CI 1.88–3.95). These data support a long-lasting impact of cortisol excess on mortality which seems to persist even after apparent successful treatment of the CD (although the possible effect of hypopituitarism also needs to be taken into account). Higher risk for mortality was noted with a higher number of treatments offered for the CD, whereas patients in remission by surgery alone had normal life expectancy.

Overall, mortality is undoubtfully elevated in patients with persistent hypercortisolemia. On the other hand, the relevant data for those in remission are not consistent. Potential factors contributing to these discrepancies include the variability in the criteria applied to define remission, in the duration of exposure to cortisol excess, in the recurrence rates, the follow-up interval, the multimodality treatment approaches used and the extensive periods covered in the published studies during which diagnosis and management of CD showed significant evolution. The impact of possible selection bias in surgical series from large specialist centers and the effect of variable degrees of hypopituitarism and its management (particularly glucocorticoid replacement) also need to be taken into account.

Main cause of reduced survival remains cardiovascular disease. Chronic hypercortisolaemia is associated with a number of cardiovascular abnormalities (visceral obesity with insulin resistance, impaired glucose tolerance, atherosclerosis, arterial hypertension, dyslipidaemia and hypercoagulability) which do not seem to reverse completely even after remission of the CD [4, 29-32] necessitating regular monitoring and tight control of cardiovascular risk factors in these patients.

Predictive factors for increased mortality in CD

Age at diagnosis

Data on the impact of age at CD diagnosis on mortality are inconsistent with some studies proposing it as an independent predictor [1, 4, 11, 13, 18, 19, 20, 28], and others not reaching similar conclusions [12, 15]. It should be noted, however, that in a large multicenter series, deceased patients had achieved remission of the Cushing's 10 years later than those who had

survived (aged 42 *vs* 34 years, $p<0.001$) [14] suggesting that exposure to cortisol excess may have a more detrimental effect in older ages.

Sex

There is no agreement on the impact of sex on mortality. Thus, it has been reported to be higher in women [1, 12], or in men [17, 18, 20], whereas in other studies, gender had no effect in survival [15, 19].

Management approaches for the CD

Patients treated with bilateral adrenalectomy for their CD have higher mortality risk [4, 19]; this may be related to the fact that this approach is usually offered to patients with primary or recurrent CD not responding to other treatment modalities; furthermore, the contribution of adrenal crises or glucocorticoid overtreatment can not be excluded. Pituitary radiotherapy has been associated with increased mortality in one [4] but not in other studies [15, 19].

Conclusions

Patients with CD have increased mortality, primarily due to cardiovascular disease and infections. Despite the advances in the diagnosis and management of this rare condition, survival can be compromised even after apparent successful treatment. Minimizing the duration and extent of exposure to cortisol excess by early diagnosis and rapid, effective therapeutic interventions, as well as close monitoring and aggressive control of cardiovascular risk factors are vital for improving outcomes.

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Table 1. Summary of studies reporting on standardized mortality ratios in patients with Cushing's disease.