Article:
Kelsall, A. and Newell-Price, J. orcid.org/0000-0002-0835-5493 (2022) Cushing mortality in remission: not out of the woods. The Journal of Clinical Endocrinology & Metabolism, 107 (10). e4232-e4233. ISSN 0021-972X

https://doi.org/10.1210/clinem/dgac341

The Journal of Clinical Endocrinology & Metabolism, 2022, **107**, e4232–e4233
https://doi.org/10.1210/clinem/dgac341
Advance access publication 01 June 2022
Commentary

Cushing Mortality in Remission: Not Out of the Woods

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Key Words: Cushing syndrome, mortality, meta-analysis, causes of death, meta-regression analysis
Abbreviations: SMR, standardized mortality ratio.

Endogenous Cushing syndrome is a rare endocrine disorder associated with significant morbidity and mortality (1, 2). Many breakthroughs have occurred since Harvey Cushing's description of a "somewhat bizarre polyglandular syndrome," and advances over the last few decades in imaging, laboratory assays, surgery, and medical therapies have led to improved remission rates and reduced mortality (3). Often, following successful surgery, we are able tell patients that their cortisol levels are very low, and reassure that many of their signs and symptoms will gradually improve. Despite remission, however, there is debate as to whether there is ongoing increased mortality. This issue has recently been addressed by Limumpornpetch et al in their extensive systematic review and meta-analysis (4).

A decade ago, a previous meta-analysis by Graversen et al analyzed 797 patients from 7 publications, the majority of whom had Cushing disease (n = 688) (4). Overall, the standardized mortality ratio (SMR) was 1.8 (95% CI, 1.3-2.7) for Cushing disease and 1.9 (95% CI, 0.9-3.9) in Cushing caused by an adrenal adenoma (n = 109). Interestingly, no significant difference was found between the mortality rate of the surgically "cured" Cushing disease group and the general population (5).

In contrast, Limumpornpetch et al showed an increased SMR across all subtypes of Cushing syndrome, including adrenal Cushing and patients in remission (4). This, the largest analysis in the field to date, included 20 study cohorts with a total of 3691 patients, among whom 1531 patients had benign adrenal causes of Cushing syndrome, over a period of years from 1958 to 2018. As would be expected, the most common cause of mortality reported was cardiovascular disease (43.4%), followed by infection (12.7%) and malignancy (10.6%), with unknown cause of death in 15.5%. The SMR in patients with active Cushing disease was significantly higher than those in remission (5.7 vs 2.3). Worse outcomes were reported in macroadenomas (SMR = 7.4) compared with microadenomas (SMR = 1.9).

This comprehensive analysis provides very important data, but also throws up a key surprise, namely the headline report of an elevated SMR in adrenal Cushing (3.34) compared with pituitary disease (2.8). Nowadays, unilateral laparoscopic adrenal surgery has a low complication rate, and a cure rate approaching 100%, in expert hands. In clinical practice, the majority of such patients then experience rapid improvements in their clinical state and relapses virtually never occur. How then may these observations be explained?

The data are not broken down into numbers of unilateral compared with bilateral adrenalectomy, and one anticipates better outcomes for the former where recovery of the hypothalamic-pituitary-adrenal axis is the norm, and this is likely to be part of the explanation. Indeed, as the authors highlight, some of the patients with Cushing disease in earlier series were treated with bilateral adrenalectomy. A significant reduction in proportion of deaths was noted post-2000 compared to pre-2000, in both the adrenal and Cushing disease groups, suggesting, reassuringly, better outcomes from modern management. Nevertheless, it is important not to be complacent as increased morbidity and mortality of both over and under adrenal replacement is well established, and indeed in this current meta-analysis, death from adrenal insufficiency across all subgroups was 3.0%. Moreover, the difference in SMR between adrenal and pituitary Cushing may suggest that hypopituitarism and requirement for other hormone replacements contributes less to SMR in Cushing disease compared with other pituitary pathologies.

Some markers of remission may not be stringent enough, and it is likely that some patients with "recurrence" of disease were never in remission. Of the patients reported to be in remission by Limumpornpetch et al it is not clear whether remission occurred after one procedure, or several. A multicenter, multinational retrospective cohort study suggested a normalized long-term survival in patients with Cushing disease "cured" by a *single* pituitary surgery; as the number of treatments increased, a corresponding reduction in survival was noted (6). These data emphasize the need for patients to be treated by high volume, experienced surgeons to ensure the best outcomes.

Another explanation for the elevated mortality in patients in remission from Cushing syndrome could be that the consequences of hypercortisolemia are not fully reversible (2). Prior studies have shown persistence of cardiometabolic risk factors even following remission (7). On the one hand,

Received: 19 May 2022. **Editorial Decision:** 27 May 2022. **Corrected and Typeset:** 22 June 2022

one would imagine that this would be exacerbated by longer duration of hypercortisolemia, with a recent analysis reporting 34 months as the median time to diagnosis (8). On the other hand, against this notion is that the time to diagnosis for patients with adrenal Cushing appears to be significantly less than those with pituitary disease (30 months vs 38 months) (8). This observation does not fit neatly with the higher mortality observed by Limumpornpetch et al in the adrenal Cushing group compared with Cushing disease; data on the degree of hypercortisolemia in these 2 groups is not available, and that too may be an important factor.

Limumpornpetch et al correctly emphasize the need for active management of cardiovascular risk factors, even in remission, to reduce mortality risk. If, however, increased mortality is driven by prior exposure to cortisol then early identification of disease becomes ever more important. This is, however, a much harder issue to address, as the early stages of hypercortisolemia may be missed by the generalist. Education of non-endocrine colleagues might reduce time to diagnosis and hence reduce length of exposure to cortisol, but having a major impact at that point in the patient pathway is very difficult to achieve. In contrast, once the diagnosis is considered by an endocrinologist it is beholden on us all to ensure that education for endocrinologists, and referral pathways for patients, are such that patients with suspected Cushing syndrome are not subjected to repeated but inconclusive and time-consuming investigation, when a rapid and timely diagnosis may be made, and definitive optimum treatment achieved, by early referral to an expert center.

While we now know significantly more about this "somewhat bizarre polyglandular syndrome," questions about Cushing syndrome remain 100 years later. Further research into length of exposure and degree of severity of disease would be helpful in further delineating their impact on mortality.

Disclosures

A.K.: no disclosures to declare. J.N.P.: Research and consultancy paid to the University of Sheffield from Crinetics, Diurnal, HRA Pharma, and Recordati.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

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