Cure of Cushing's Disease: Still an Elusive Goal?

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The goals of treatment of patients with Cushing's disease (CD) include the resolution of hypercortisolism, the resection of tumor mass, the restoration and preservation of normal pituitary function, the early detection and prompt management of hypercortisolism-associated comorbidities, aiming at reversing symptoms and signs and ultimately restoring longevity to that of the general population.

We have come a long way towards achieving these goals in the 100 years since Cushing's original description of the index case of the now eponymous disease (1, 2). Indeed, the 5-year survival rate of patients with CD was 50% in Cushing's era, despite his pioneering efforts and meticulous surgical technique (1, 2). Similar outcomes were reported by Plotz and colleagues in the early 1950s (3). Since then, refinements in the surgical and medical management of patients with CD have led to substantial improvements in patient outcomes, with 5-year survival rates exceeding 95% in the modern era. About a decade ago, a meta-analysis reported that the standardized mortality rate of patients with CD in remission was not significantly higher than in the general population (4).

Despite these welcome advances, the outlook for patients with CD remains uncertain and often guarded. Recurrence of hypercortisolism is not uncommon in this population, exceeding 25% to 30% on long-term follow-up (5). Even among patients with CD in remission, residual symptoms and signs, including psychiatric manifestations, cognitive dysfunction, and abnormalities in body composition, are not uncommon. In contrast to earlier data (4), a large, multicenter study of patients with CD in long-lasting remission recently documented significantly increased all-cause mortality in this population (6). Mortality secondary to cardiovascular disorders was increased but mortality secondary to malignancies was not (6).

Against this backdrop, the nationwide study by Papakokkinou et al. reported on the incidence of several comorbidities associated with CD in a large Swedish patient population (7). As anticipated, patients had an increased standardized incidence ratio for myocardial infarction, venous thromboembolism, and fracture during a 3-year period before the diagnosis of CD was made. Perhaps more unexpectedly, patients with CD in long-lasting remission had a significantly elevated standardized incidence ratio for stroke, venous thromboembolism, and sepsis. These observations raise substantial concerns regarding long-term outcomes in this population and suggest the need for changes in management of patients with CD in endocrine remission. However, the findings of this study do not provide clear-cut insights into the mechanisms that account for the persistently elevated risk of multiple comorbidities in this population.

Many factors may contribute to the increased cardiovascular risk of patients with CD, including central obesity, hyperglycemia, hypertension, dyslipidemia, cardiomyopathy, coagulopathy, endothelial dysfunction, and atherosclerosis, among others. There is evidence that some of these processes and conditions may not be fully reversible despite biochemical remission of hypercortisolism. For example, some abnormalities in cardiac function have been reported to persist in patients with Cushing's syndrome who were in remission for several years, despite demonstrating

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initial improvement in several echocardiographic indices (8). There is also evidence that abnormalities in brain structure and function may persist in patients with CD in remission. Of note, neuropsychiatric manifestations were not examined in the study by Papakokkinou et al. (7).

How can we account for the increased morbidity and mortality risk in patients with CD in remission? It is conceivable that some pathologic processes associated with hypercortisolism may not be fully reversible once initiated, and may persist or even progress despite endocrine remission. However, other potential explanations may also exist. It is possible that the management of cardiometabolic risk factors, such as hypertension, hyperglycemia, and dyslipidemia, may have not been aggressive enough in some patients with CD. Use of higher glucocorticoid replacement doses in some patients with CD who are in remission and have not yet recovered normal activity of their hypothalamic–pituitary–adrenal axis could conceivably contribute to an increased cardiovascular risk, as has been documented in previous studies of patients with hypoadrenalism of diverse etiologies. In addition, higher glucocorticoid replacement doses could plausibly account for the increased risk of sepsis in the study of Papakokkinou et al. among patients in remission (7). Pituitary hormone deficiencies may have not been appropriately replaced in some patients with CD in remission, thereby contributing to their increased morbidity and mortality risks. Finally, it is conceivable, albeit unproven, that recurrent, low-level hypercortisolism might occur undetected in some patients with CD thought to be in remission and increase their risk of hypercortisolism-associated comorbidities. Criteria for endocrine remission were heterogeneous in the study by Papakokkinou et al. (7), likely reflecting test evolution over time but also raising the possibility that subtle hypercortisolism might potentially occur among some patients thought to be in remission based on less stringent tests. Clearly, more studies are needed in order to fully elucidate the factors and mechanisms underlying diverse comorbidities among patients with CD in remission.

In the meantime, the findings of the study by Papakokkinou et al. (7) should raise awareness of an important clinical problem in patients with CD in remission and suggest the need for an aggressive approach to case finding and thorough management of associated comorbidities. Moderation of glucocorticoid replacement doses to avoid excess, and stringent control of hypertension, dyslipidemia, and hyperglycemia should be implemented in these patients. The role of other interventions aimed at reducing cardiovascular risk, such as antiplatelet and anticoagulation therapies, requires further study in this population. Mechanistic studies are needed in order to elucidate the underlying pathophysiologic mechanisms and pathways that drive comorbidities in patients with CD who are in remission. The establishment and recognition of Pituitary Tumor Centers of Excellence may foster research in the field and facilitate the coordination of care of patients with CD in remission. These patients may likely benefit from multidisciplinary evaluations by several subspecialists in nonendocrine fields, including cardiovascular medicine, neurology, and psychiatry, among others, in addition to comprehensive neuroendocrine care.

We have come a long way since Harvey Cushing's seminal description of CD. Indeed, major advances in the diagnosis and management of this challenging condition have occurred over the past one hundred years and have led to substantially improved patient outcomes. The study by Papakokkinou et al. (7) tells us that we still have a long way to go.

Additional Information

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