Hypopituitarism—needs modern individualized treatment

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Patients with hypopituitarism have an excess mortality, which was first described in the *Lancet* in 1990 [1]. This novel finding changed the field and the perspective of hypopituitarism and was later confirmed by other studies [2]. Jasim et al. have conducted a commendable review and meta-analysis of mortality in adults with hypopituitarism [3]. This meta-analysis also confirmed that patients with hypopituitarism have an overall excess mortality, although the groups at enhanced risk are women and patients diagnosed at young age. The standardized mortality ratio (SMR) of hypopituitary patients (1.8–1.9) can be compared to that of morbidly obese patients (1.6), showing the very real effect of hormonal deficiencies on life expectancy [1, 2, 4]. We believe that the source of the excess mortality originates from non-physiological replacement therapy, untreated deficiencies, local effects of the tumor itself, and adverse effects of tumor treatment (mostly radiotherapy) [2, 5–7].

With hypopituitarism, women have an increased mortality and morbidity compared to men [7, 8]. The exact cause for this has not yet been determined but is likely to be due to less physiological replacement therapy and higher frequency of untreated gonadotropin deficiency. A few studies have shown that replacement therapy with sex hormones may be more frequently neglected in women than in men [1, 2]. Women have also been shown to receive higher replacement doses of glucocorticoids per kg than men [9]. Treatment differences and hypopituitarism result in an increased vascular risk in women

(e.g. increased waist/hip ratio, stiffness of arteries) compared to men [10, 11]. All these aspects result in an excess mortality in women that increases with the duration of the disease [12].

Young age at diagnosis has also been found to be a negative predictor of mortality in patients with hypopituitarism [2, 3, 7]. Since many of the studies in this field have included patients with craniopharyngioma, this might explain some, but not all, of the effect on mortality in young patients. Patients with craniopharyngioma have a lower mean age at diagnosis (35 vs. 58 years) and a much higher mortality [SMR: 3.8 (95% CI 2.9–5.0) vs. 1.1 (95% CI 1.0–1.2)] compared to the patients with non-functioning pituitary adenoma [7, 13]. The additive effect of long-term hormonal deficiencies seems to worsen the overall health [7].

The meta-analysis by Jasim et al. suggested that there is a trend for higher mortality in patients without growth hormone (GH) replacement therapy [3]. The clinical picture of GH deficiency (e.g. increased fat mass, reduced lean mass, osteopenia, an unfavorable lipid profile, reduced muscle strength, fatigue) has been recognized since the early 1990s [14]. Long-term studies on the effect of GH replacement therapy have since shown an improvement in many of these features, such as improved lean body mass, decreased body fat, beneficial effects on plasma lipids, positive effects on intima media thickness, improvement in bone mineral density, and better quality of life [15]. Lately, partly due to a recently published study, a growing body of evidence is showing that GH replacement therapy is associated with reduced excess mortality or normalized mortality compared to the general population [5, 16]. We have shown that GH replacement therapy is associated with normalized mortality among over 400 non-functioning pituitary adenoma patients receiving or not receiving GH replacement, who were followed for 10 years [5].

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Traditional glucocorticoid replacement with daily hydrocortisone doses of 25–30 mg/day have been shown to increase mortality and morbidity as well as leading to an adverse metabolic profile in hypopituitary patients [6, 17]. The daily replacement dose should be compared to the endogenous production level in normal subjects, estimated to be approximately 10 mg/day [18]. A promising new glucocorticoid replacement therapy, based on a dual-release tablet, seems to have a more circadian-based serum cortisol profile and reduces body weight, blood pressure, and improves glucose metabolism [19]. Hopefully, new therapies, which more closely mimic the physiological pattern, can decrease the negative effects of glucocorticoid deficiency.

The meta-analysis by Jasim et al. was well conducted overall, but a few aspects need to be commented [3]. For example, at least half of the studies included in the meta-analysis had a significant proportion of patients with an etiology resulting in high inherent excess mortality, such as craniopharyngioma, secreting adenomas (adrenocorticotrophic hormone or GH), and malignancies. These etiologies have, of course, an effect on mortality not originating from the hypopituitarism. In addition, it is difficult to divide the studies into GH-treated and untreated cohorts since most cohorts were mixed; for example, a significant portion of the patients in the study by Olsson et al. was receiving GH replacement therapy.

In conclusion, hypopituitarism is a severe disease, with mortality comparable to morbidly obese patients. We therefore believe that all hypopituitary patients, in second decade in the 21st century, have the right to be managed and treated by multi-specialist teams including especially endocrinologists, neurosurgeons, radiologists, and pathologists. Up-to-date care for these patients should include individualized and continuously evaluated replacement therapy. We believe that the replacement regime should, if no contra-indication exists, include modern glucocorticoid, levothyroxine, sex hormone, and GH replacement therapy. Additionally, we need to put more effort into targeted improvement in the management of women and young patients with hypopituitarism.

Compliance with ethical standards

Conflict of interest D.S.O. has been a consultant for Novartis, Sandoz, Ipsen, and Pfizer. B.Å.B. has no conflict of interest to declare.

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