Epidemiology of Cushing's Syndrome

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Abstract
Overt Cushing's syndrome is a rare disorder with an annual incidence of 2–3/million of which benign adrenal adenomas account for 0.6/million. The female:male ratio is 3:1. Preliminary data indicate a high proportion of subclinical Cushing's syndrome in certain risk populations such as patients with type 2 diabetes or osteoporosis. The clinical implications of these observations are presently unclear. Surgery remains first line treatment for overt disease and initial cure or remission is obtained in 65–85% of patients with Cushing's disease. Late recurrences, however, occur in up to 20% and the risk does not seem to plateau even after 20 years of follow-up. A 2- to 3-fold increase in mortality is observed in most studies, and this excess mortality seems confined to patients in whom initial cure was not obtained. Cushing's syndrome continues to pose diagnostic and therapeutic challenges and life-long follow-up is mandatory.

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Cushing's syndrome is considered a rare disorder although data on accurate rates of its incidence and prevalence in the general population are few [1]. Some of the clinical features are shared with far more common conditions such as type 2 diabetes, the metabolic syndrome, and polycystic ovary syndrome. Moreover, the incidence of these latter conditions seems to increase rapidly which probably represents the combined result of a true rise in the incidences and increased awareness about the diagnoses. For these reasons alone, it is foreseeable that Cushing's syndrome in the future will be diagnosed at an earlier stage and perhaps also more frequently.

In addition, screening programs for Cushing's syndrome in pertinent target populations indicate a substantial prevalence of undiagnosed or subclinical cases [2–5], and there is also accumulating evidence to suggest subclinical Cushing's syndrome in a large proportion of cases of adrenal incidentalomas [6, 7].

Notwithstanding this, overt Cushing's syndrome is a serious condition with an excess mortality that calls for prompt treatment [1]. Unfortunately, the risk of recurrence after initial surgical cure of ACTH-producing pituitary adenomas is high and necessitates lifelong monitoring [8].

**Fig. 1.** Demographic and epidemiological data on Cushing's syndrome based on a nationwide Danish survey (1985–1995). Nonmalignant causes exclude all ectopic tumors and adrenal carcinomas. Annual incidence of nonmalignant causes = 2.3/million; female:male ratio = 3:1; overall SMR for nonmalignant causes = 3.68 (95% CI 2.34–5.33). The figure is based on previously published data [1] and is reproduced with permission: copyright 2001, The Endocrine Society.
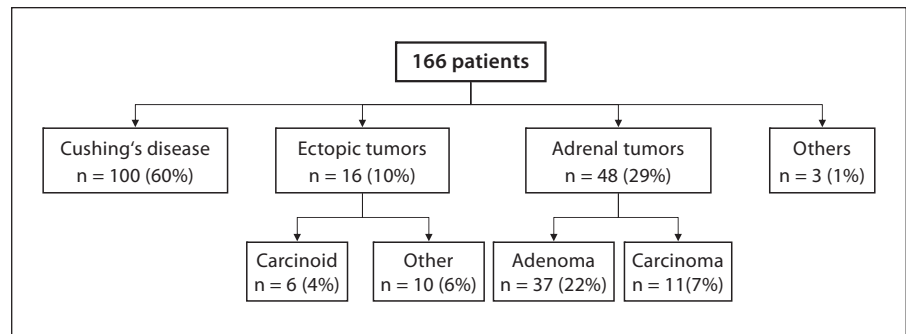
Fig. 2. Sex distribution in Cushing's syndrome based on a nationwide Danish survey (1985–1995). Gender distribution (%). The figure is based on previously published data [1] and is reproduced with permission: copyright 2001, The Endocrine Society.
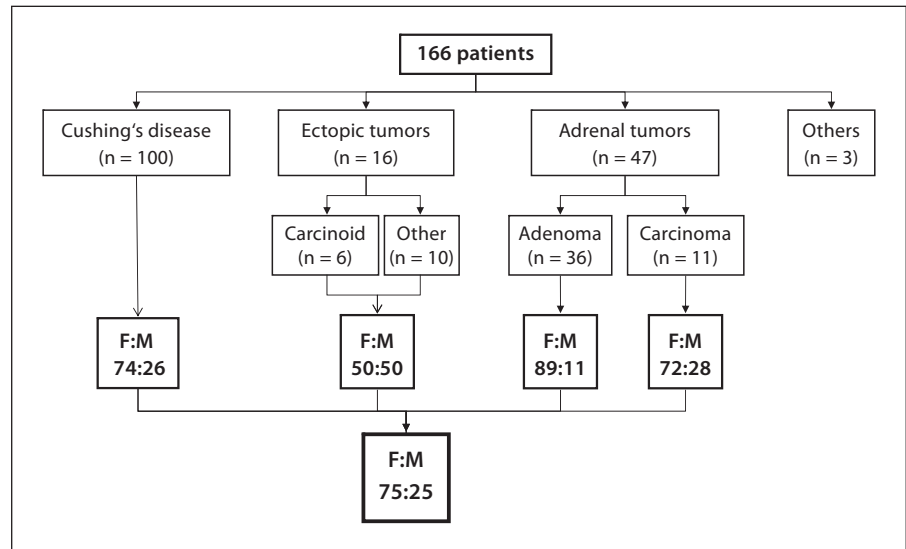
This review will focus on recent data regarding the epidemiology of Cushing's syndrome, the outcome of treatment and the risk of recurrence.

Incidence and Prevalence

The assessment of rates of incidence and prevalence depends on a number of factors including a reliable and retrievable diagnosis, and knowledge about the catch up area in which the diagnosis is made. The diagnosis and differential diagnosis of Cushing's syndrome are far from trivial and beyond the scope of this paper [9]. A study from a defined region in Spain reported an annual incidence of Cushing's disease of 2.4 cases per million and a prevalence of 39.1 cases per million [10]. In accordance with observations made in other pituitary disorders [11], the authors observed an almost linear increase in the prevalence during the study period from 1974 to 1992 [10].

A recognized problem with epidemiological surveys from specialized centers is whether the figures are representative for the general population. For this reason a nationwide Danish study was undertaken, which profited from the fact that every Danish citizen holds a unique ID number that makes it easy to retrieve and combine pertinent data regarding health, disease and death from different registries [1]. The hospital record for each case was ultimately scrutinized to validate the diagnosis and retrieve pertinent demographic data. The annual incidence of Cushing's disease was 1.2–1.7/million per year with no difference in the rates between 1985–1990 and 1991–1995 (fig. 1). The annual incidence of benign adrenal adenomas and adrenal cancers was 0.6/million and 0.2/million, respectively. The calculated annual incidence of Cushing's syndrome induced by a nonmalignant cause was 2.3/million [1]. The median age at first admission was 41.4 years (range 3.6–77.7), and the female:male ratio was 3:1 (fig. 2).

By contrast, much higher figures are recorded from screening of patients with type 2 diabetes or osteoporosis,

in whom the prevalence of occult or subclinical Cushing's syndrome is 5–10% [2–5]. In general, patients with subclinical Cushing's syndrome in these studies also displayed a more severe clinical picture as compared to patients without evidence of cortisol hypersecretion and this distinction also exists among patients with adrenal incidentalomas [6, 7].

Outcome of Surgery for Cushing's Disease

In general, the initial remission rate following pituitary surgery (almost exclusively transsphenoidal procedures) ranges between 65 and 90% [1, 8, 12–15]. The main positive predictor of outcome seems to be the identification of an adenoma either by imaging, during surgery or with immunohistochemistry. Negative predictors include invasive tumors, absence of a visible tumor, and the postoperative occurrence of elevated or only transiently suppressed cortisol levels. The importance of an experienced and dedicated surgeon has not been specifically addressed in these studies, although it seems that large series with a single surgeon are associated with an outcome above the average [8, 13].

Regardless of the initial outcome, all studies demonstrate that the risk of recurrence is relatively high and continues for many years [1, 12, 14, 15]. In one study, high pretreatment levels of cortisol and ACTH were significant predictors of relapse [15], but this was not reproduced in a study comprising 25 European centers [12]. In both studies, however, elevated or nonsuppressed cortisol and ACTH levels were predictive of relapse, whereas a more sustained need for postoperative glucocorticoid replacement was associated with a lower risk of recurrence [12]. The multicenter study also revealed that recurrence continued at a constant rate over the ten years of observation [12], and similar observations were made in a recent single-center study from the US [13]. The risk of recurrence ranges between 0 and 20%, but it is noteworthy that the reported risk – if anything – seems to be higher in the more recent studies.

Mortality in Cushing's Syndrome

The Danish survey observed an excess mortality (SMR) of 3.68 (95% CI: 2.34–5.33) in patients with nonmalignant Cushing's syndrome (fig. 1) [1]. Pretreatment cortisol levels did not differ between survivors and nonsurvivors and the gender distribution was equal. Interest-

ingly, mortality was also increased in the subgroup of patients with benign adrenal adenomas (SMR 3.48, 95% CI 0.95–8.90). In the subgroup of patients with Cushing's disease the mortality rate was much higher among cases in which cure was not achieved or in which an ACTH-producing pituitary adenoma was not proven histologically [1]. Indeed, no excess mortality was observed in patients with recurrence-free Cushing's disease (SMR 0.31, 95% CI 0.01–1.72). A surprisingly large number of deaths among the patients with nonmalignant Cushing's syndrome occurred within the first year of admission. As expected, patients with adrenal carcinomas and patients with ectopic tumors had a very poor prognosis [1]. The Danish mortality data for Cushing's disease agrees with both previous and more recent data [10, 14]. In a Spanish study, a major cause of death was vascular disease, and hypertension as well as impaired glucose metabolism were independent predictors of mortality [10]. A recent Dutch study compared mortality in Cushing's disease versus patients with nonfunctioning pituitary adenomas (NFPA); the SMR in Cushing's disease was 2.39 (95% CI 1.22–3.9) as compared to a SMR of 1.24 (95% CI 0.85–1.74) in patients with NFPA. In a subsequent regression analysis the mortality rate remained increased in Cushing's disease as compared to NFPA after adjustment for age, gender, radiotherapy and hypopituitarism [14]. Of interest, the latter study also reported that excess mortality was confined to patients with persistent disease [14]. Two additional studies comprising Cushing's syndrome and Cushing's disease did not record a significant increase in the mortality rate of their patients as compared to the background population [16, 17].

Discussion

Cushing's syndrome in its classic sense remains a rare condition associated with diagnostic and therapeutic challenges and an excess morbidity and mortality. The Danish survey probably provides the most accurate estimate about the incidence rates of overt Cushing's syndrome owing to the nationwide approach and the infrastructure of that particular country [1]. The population, however, consisted mainly of Caucasians so it does not take ethnic differences into account.

The fact that the syndrome remains incipient for 3–6 years and that many of the symptoms are common to those of highly prevalent conditions such as T2DM, hypertension and the polycystic ovary syndrome raise the question whether overt Cushing's syndrome just repre-

sents the tip of the iceberg. In other words: is Cushing's syndrome underdiagnosed? Indeed, a number of screening studies reveal that a very high proportion of patients – i.e. up to 10% – with either T2DM [2, 3, 5], osteoporosis [4], or adrenal incidentalomas [7] show biochemical evidence of cortisol hypersecretion. Moreover, cortisol hypersecretion seemed also associated with more pronounced disease and certain phenotypical characteristics of overt Cushing's syndrome [3, 7]. These findings raise several new questions. First, do these cases represent incipient stages that eventually develop into 'classic' Cushing's syndrome? Second, what are the therapeutic implications? Third, should we screen certain high-risk patient groups, e.g. obese patients with poorly controlled T2DM, for Cushing's syndrome? When considering how rarely the diagnosis is being made at present – less than 3 new cases per million each year – it would seem unlikely that up to 7% of patients with T2DM have undiagnosed or occult Cushing's syndrome. The majority probably represents a new clinical entity with mild or borderline hypercortisolism. If one chooses to perform screening programs, which tests should be used? How many of such patients will eventually benefit from pituitary or adrenal surgery? It is clearly an area that merits future attention but it should be in the form of structured programs that allows a balanced cost-benefit analysis. These concerns were also addressed in a recent guideline paper issued by the Endocrine Society [9].

The outcome of transsphenoidal surgery for Cushing's disease is generally favorable with immediate cure rates between 65 and 90% and very low perioperative mortality rate. Surgical experience is undoubtedly of importance although no direct evidence is available. In the Danish study, where at least 3 different surgeons were used for 68 operations, the immediate cure rate was 66.2%, whereas a recent study from the US reported an immediate cure rate of 85.6% in 215 patients all of whom were operated by a single surgeon [1, 13]. But regardless of a successful immediate outcome a high risk of late recurrences remains for decades, which necessitates lifelong follow-up.

Cushing's syndrome is still today associated with increased mortality. As expected, this is more pronounced in patients with a malignant disease [1], but an excess mortality is also recorded in patients with Cushing's disease [1, 10, 14] and in patients with benign adrenal adenomas [1]. In the Danish study, the risk of death from nonmalignant Cushing's syndrome was highest during the first year after initial admission and a number of deaths occurred before a specific treatment could be undertaken [1]. By contrast, the mortality rate was not significantly increased in patients with Cushing's disease who were cured after initial surgery [1, 14]. It is obviously reassuring that treatment reduces mortality, but the data also underscores the necessity to implement treatment as soon as possible and to pay special attention to patients with Cushing's disease, who are not cured after initial surgery. The proper therapeutic approach in such cases remains open for debate, but the option for bilateral adrenalectomy should not be forgotten.

In conclusion, Cushing's syndrome remains a diagnostic and therapeutic challenge. The available data demonstrate that early and curative treatment does improve survival, but late recurrences after initially successful pituitary surgery occur even in the best centers.

Disclosure Statement

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