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Context: Patients with hypopituitarism have an increased standardized mortality rate. The basis for this has not been fully clarified.

Objective: To investigate in detail the cause of death in a large cohort of patients with hypopituitarism subjected to long-term follow-up.

Design and Methods: All-cause and cause-specific mortality in 1286 Swedish patients with hypopituitarism prospectively monitored in KIMS (Pfizer International Metabolic Database) 1995–2009 were compared to general population data in the Swedish National Cause of Death Registry. In addition, events reported in KIMS, medical records, and postmortem reports were reviewed.

Main Outcome Measures: Standardized mortality ratios (SMR) were calculated, with stratification for gender, attained age, and calendar year during follow-up.

Results: An excess mortality was found, 120 deaths vs 84.3 expected, SMR 1.42 (95% confidence interval: 1.18–1.70). Infections, brain cancer, and sudden death were associated with significantly increased SMRs (6.32, 9.40, and 4.10, respectively). Fifteen patients, all ACTH-deficient, died from infections. Eight of these patients were considered to be in a state of adrenal crisis in connection with death (medical reports and post-mortem examinations). Another 8 patients died from de novo malignant brain tumors, 6 of which had had a benign pituitary lesion at baseline. Six of these 8 subjects had received prior radiation therapy.

Conclusion: Two important causes of excess mortality were identified: first, adrenal crisis in response to acute stress and intercurrent illness; second, increased risk of a late appearance of de novo malignant brain tumors in patients who previously received radiotherapy. Both of these causes may be in part preventable by changes in the management of pituitary disease. (*J Clin Endocrinol Metab* **98: 1466–1475, 2013**)

Most previous studies have found all-cause mortality in patients with hypopituitarism to be increased (1). The excess standardized mortality rate (SMR) has largely been explained by cardiovascular/cerebrovascular diseases (2, 3). In addition, respiratory disease has been observed and discussed in one study (4) and gastrointestinal disease has been observed in another study (5). Malignancy-related death has been reported to be either similar (3, 4, 6, 7) or increased, in particular, in young subjects (5, 8–10). The underlying cause of hypopituitarism and its treatment, the extent of endocrine deficiencies and their treatment, as well as the reference population used are likely to have influenced the variable outcomes.

Recently, a modest increase in overall mortality (SMR 1.13, 95% confidence interval [CI] 1.04–1.24) was observed in a noninterventional, pharmacoepidemiological study in hypopituitary patients treated with GH (Pfizer International Metabolic Database [KIMS]; Pfizer Inc, New York, New York) compared with World Health Organization general population estimates (11). A younger attained age, female gender, an underlying diagnosis of craniopharyngeoma, Cushing's disease and aggressive central nervous system (CNS) tumors, and the presence of diabetes insipidus were associated with premature death.

In the present study, comparison with the national Cause of Death Register (CDR) matched for age, sex, and calendar year was complemented by detailed review of medical charts and postmortem examinations. This procedure enabled a most comprehensive understanding of events leading to death and provided new information.

Patients and Methods

The Swedish CDR, initiated in 1961, provides the basis for official statistics on causes of death. More than 99% of deaths are reported to the Register. The CDR uses International Classification of Diseases-10 (ICD-10) codes to assign an underlying (main) cause of death and contributing causes. The Swedish KIMS database, which was started in 1994, contains information on patients with childhood or adult-onset GH deficiency (GHD), treated with Genotropin or untreated. The normal routine is that death is reported to KIMS by the treating physician as an event and a comment in free text.

As of 2 June 2008, 1335 patients from 36 clinics were part of the Swedish KIMS database. All but 4 patients had received GH while in KIMS. We identified patients that died after KIMS entry by asking the participating clinics to send birth dates including the unique last 4-digit patient numbers to the CDR. Dates of birth were provided in 1286 of 1335 patients (in 19 patients the 4-digit personal identifiers were not correctly entered; another 30 patients were from nonresponder clinics). The end-of-search date in the CDR was set to 31 March 2009. Total number of patient-years from KIMS entry to date of death or March 31, 2009 was 11 450, representing a median follow-up time of 9.55 years (5th to 95th percentile 2.35–13.49). A total of 120 patients

were found to have died. Comparison on causes of death was based on the diagnoses in the CDR. Event reports and comments on deaths by the investigators provided complementary information. Medical charts and, when available, autopsy reports were reviewed in all cases, with the exception of deaths due to a malignant tumors outside the CNS, deaths due to cardiovascular/cerebrovascular accidents, and death due to external causes, provided that the cause of death on the death certificate and the KIMS event report were congruent.

The initial analysis was based on CDR ICD-10, whereby main categories unexpectedly showed benign neoplasm as a prevalent cause of death (n = 14). These cases were therefore examined in detail. One death was due to a myeloproliferative syndrome; one death was due to a growing meningeoma, and 12 had a benign pituitary tumor (ICD-10 code D352, n = 5; D444, n = 4; D443, n = 3) as the cause of death. Only 3 of these 12 patients had died from the pituitary tumor itself or its treatment. The other 9 cases were recoded according to the contributing cause of death on certification (cardiovascular disease in 2, cerebrovascular disease in 1, degenerative diseases of the CNS in 2, infections in 4). These diagnoses agreed with the causes of death reported by the KIMS physicians. Verifications were obtained from medical charts, and when available, autopsy reports.

On review of the accumulated information from the CDR, KIMS, medical charts, and autopsy reports, deaths from infections and brain cancer seemed more frequent than anticipated. The spectrum of malignancy was therefore examined (see *Results*). A composite endpoint "All infectious diseases" was made to include the following CDR ICD-10 codes: A08–09, A40–41, A46, A48–49, B99, J00–J22, G00–G09, and K52.

Statistical methods

Mortality rates in the study cohort were compared to that in the general Swedish population using the SMR, defined as the ratio between the observed and expected number of deaths. Observed death cases were caught by record linkage against the CDR for the period from KIMS entry date to March 31, 2009. The expected number of deaths was computed based on mortality rates in the Swedish general population published by the national Board of Health and Welfare (http://www.socialstyrelsen.se/register/dodsorsaksregistret) and the number of patient-years in the Swedish KIMS study cohort, as defined above. Stratification was performed by gender, 5-year attained age classes (15–19, . . ., 80–84, 85+), and single calendar year (1995, 1996, . . ., 2009) during the course of follow-up. Additional control for attained age, etiology of hypopituitarism, and gender by means of regression methods was necessary in the SMR comparisons due to differences between patient groups (ie, childhood and adult-onset patients) and large variation in rates of background mortality. The observed number of deaths was assumed to follow a Poisson distribution. Byar's approximation formula was used to calculate the 95% CI (12). For control of confounding factors, Poisson regression (PROC GENMOD; SAS software version 9; SAS, Marlow, United Kingdom) was used and fitted on grouped data. Expected number of cases was set as offset. Mean values for each category were used for numerical variables. *P* values from significance tests were likelihood-based. Significance level was set at $P < .05$.

The study was approved by the Ethics Committee, Sahlgrenska Academy, Gothenburg, Sweden.

Table 1. Distribution of Cause of Pituitary Insufficiency and Hormone Replacement Therapy in 1286 Patients

	Childhood Onset	Adult Onset	Total
Total no. (% males)	378 (55.0)	908 (51.3)	1286 (52.4)
Mean age at KIMS entry (SD)	27.0 (9.4)	52.2 (12.5)	44.8 (16.3)
Etiology, %			
Idiopathic/congenital	141 (37.3)	94 (10.4)	235 (18.3)
Craniopharyngioma	79 (20.9)	59 (6.5)	138 (10.7)
Adenoma (nonfunctioning pituitary adenoma, prolactinoma, other)	14 (3.7)	510 (56.2)	524 (40.7)
Cushing's disease	10 (2.6)	53 (5.8)	63 (4.9)
Acromegaly	0 (0)	30 (3.3)	30 (2.3)
Other benign pituitary/hypothalamic lesions	7 (1.9)	32 (3.5)	39 (3.0)
Malignant brain tumors	77 (20.4)	26 (2.9)	103 (8.0)
Hematologic malignancies	20 (5.3)	3 (0.3)	23 (1.8)
Other malignant tumors	2 (0.5)	1 (0.1)	3 (0.2)
Other	28 (7.4)	98 (10.8)	126 (9.8)[a]
Missing	0 (0)	2 (0.2)	2 (0.2)
Replacement with (%)			
Glucocorticoids[b]	47.4	64.3	59.3
Thyroxine	67.7	71.9	70.7
Sex hormones	62.7	77.6	73.2
GH	99.2	99.9	99.7
Desmopressin	26.3	18.6	20.9

[a] Sheehan's syndrome, 26; traumatic brain injury/head trauma, 18; Langerhans cell histiocytosis and other granulomatous infiltrations, 14; lymphocytic hypophysitis, 13; vascular causes, 10; CNS infections, 7; various other etiologies, 38.

[b] Last reported hydrocortisone equivalent dose, mg/d; 20 (10–40) median, 5th and 95th percentile.

Results

The characteristics of the 1286 (674 men) patients in the study cohort are detailed in Table 1. Mean age at KIMS entry was 44.8 (SD 16.3) years and was similar between male and female patients (data not shown). About one-third of the patients had a childhood onset of hypopituitarism. At entry into the database, their age was 27.0 (SD 9.4) years vs 52.0 (SD 12.5) years in the adult-onset patients. The underlying causes of disease and the extent of hormonal replacements differed among childhood and adult-onset patients. Of patients with benign intracranial lesions (functioning/nonfunctioning pituitary adenoma, craniopharyngioma), 36.6% (277/756) had received cranial radiotherapy. This treatment had been given a median of 24.8 (range 0.9–49.8) years before study end. Time since radiotherapy in patients treated for malignant brain tumors was 20.4 (range, 9.8–50.2) years.

At KIMS entry, hypertension was reported in 205 (205/1286 = 16%) patients, diabetes mellitus in 75 (6%), malignancy (other than the etiology of hypopituitarism) in 61 (5%), coronary heart disease in 60 (5%), stroke in 49 (4%), and epilepsy in 29 (2%) patients. Stroke was the only serious comorbidity accompanied by a higher risk of death during the observed period, 21 vs 7.1 expected, SMR 2.95 (95% CI 1.82–4.50, $P < .0001$).

Overall mortality

The observed number of deaths was higher than the expected, 120 vs 84.3, SMR 1.42 (CI 1.18–1.70). SMR in

women was 1.63 (CI 1.18–2.18) vs 1.33 (CI 1.05–1.66) in men ($P = .34$). Relative excess mortality was particularly evident in patients before an attained age of 40 years, where the SMRs were 7.5–9.6 (Figure 1). For patients with a benign pituitary tumor including craniopharyngioma as the etiology of hypopituitarism (n = 794), the SMR was 1.35 (CI 1.08–1.65) based on 92 observed and 68.35 expected number of cases. Body mass index and smoking habits (17.8% were smokers) were not associated with systematic variations in risk after adjustments for age and gender. SMR for childhood onset of GHD was 2.25 times higher than for adult-onset GHD after adjustment for attained age and gender ($P = .01$). However, after additional adjustment for etiology of hypopituitarism, this SMR ratio was reduced to 1.35 times higher (CI 0.64–2.85; $P = .43$). These observations implicate that the estimated SMRs for childhood and adult-onset patients are similar if patients have the same attained age and the same causes of hypopituitarism.

Cause-specific mortality

After assignment to the de facto causes of death in the 12 cases of benign pituitary tumors (see *Patients and Methods*), SMR for the main categories of the ICD-10 codes were calculated (Table 2). The causes of death with significantly increased SMRs were benign neoplasms (n = 5), diseases of the respiratory system (n = 10), diseases of the digestive system (n = 9), and symptoms, signs, and
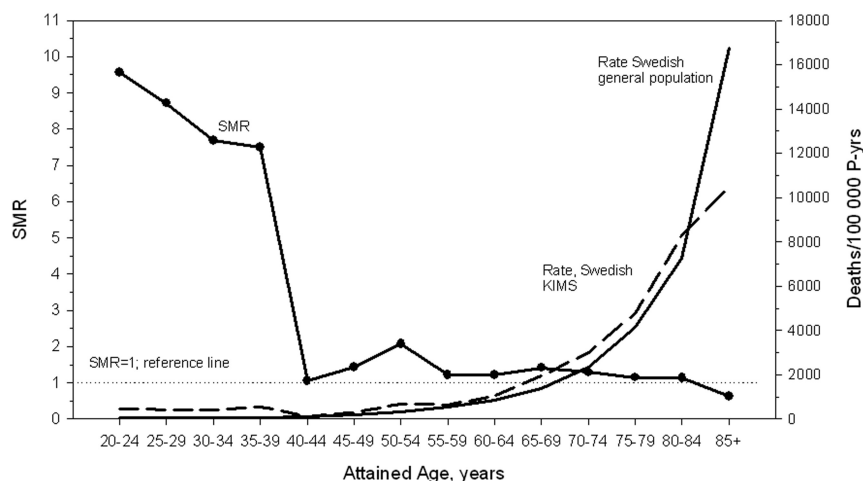
Figure 1. Relationship between SMR (closed squares) and rates expressed as number of deaths per 100 000 person-years in KIMS (broken line) and number of deaths per 100 000 person-years in the Swedish general population (solid line) by attained age during follow-up in 5-year classes. The dotted line at SMR = 1 represents the point at which mortality is equivalent to that in the Swedish general population.

abnormal clinical and laboratory findings not elsewhere classified ("ill-defined," n = 5).

The composite endpoint "All infectious diseases" resulted in a calculated SMR of 6.32 with 13 observed vs 2.06 expected cases (CI 3.36–10.8). This was supported by examination of individual death certificates that showed that the 13 patients had died from infections, comprising acute infectious gastroenteritis (confirmed by autopsy and identification of infectious agents) in 3, pneumonia in 6, erysipelas with septicemia in 1, acute

epiglottitis in 1, bacterial meningitis in 1, and multiple infections in a patient with HIV in 1. In addition, but not included in the SMR calculation, another 2 patients had been reported incorrectly to the CDR as vascular causes of deaths: acute pulmonary embolism and cardiosclerosis, respectively. However, postmortem examinations, performed because of sudden/ unexpected deaths, had revealed infectious causes: acute purulent tracheobronchitis, and gastroenteritis caused by calici virus, respectively. Thus, in total 15 patients had de facto died from infections.

SMR for deaths from diseases of the circulatory system (n = 29) and malignant neoplasms (n = 27) (ie, the most frequent causes) were similar to that of the Swedish population (Table 2). For specifically studied cancer causes, there was an increased risk of death from brain tumors with an SMR of 9.40 (CI 4.50–17.3). There were no increased SMRs for other cancers in digestive organs, lung, breasts, or prostate (Figure 2).

Of the 5 patients with "Other ill-defined/unknown cause of death," 4 were found dead at home. Two of these were treated for psychiatric diseases; autopsies were not performed due to decay. One patient likely died from ar-

Table 2. Cause-specific Mortality Main Subcategories in 1286 Patients Followed for 11 450 Patient-years

Cause of Death, ICD10	Number of Observed Deaths[a]	Observed/Expected Deaths[a]	95% CI[a]
00–Y98. All causes	120	1.42	1.18–1.70
A00–B99. Certain infectious and parasitic diseases	3	2.85	0.57–8.34
C00–C97. Malignant neoplasms	27	0.92	0.61–1.34
D00–D48. Benign neoplasms	5	8.76	2.82–20.4
E00–E90. Endocrine nutritional and metabolic diseases	4	1.82	0.49–4.66
F00–F99. Mental and behavioral disorders	2	0.84	0.09–3.05
G00–G99. Diseases of the nervous system	5	2.05	0.66–4.78
I00–I59 and I70–I99. Diseases of the heart and cardiovascular system	29	1.21	0.81–1.74
I60–I69. Cerebrovascular diseases	11	1.82	0.91–3.26
J00–J99. Diseases of the respiratory system	10	2.19	1.05–4.03
K00–K93. Diseases of the digestive system	9	2.90	1.32–5.50
N00–N99. Diseases of the genitourinary system	2	2.58	0.29–9.31
R00–R99. Symptoms signs and abnormal clinical and laboratory finding not elsewhere classified	5	3.41	1.10–7.95
V01–Y98. External causes of morbidity and mortality	8	1.39	0.60–2.73
Sum of ICD10 categories H, L, M, O, P, Q	0	0	—

Abbreviations: H, diseases of the eye and adnexa or diseases of the ear and mastoid process; L, diseases of the skin and subcutaneous tissue; M, diseases of the musculoskeletal system and connective tissue; O, pregnancy, childbirth, and the puerperium; P, certain conditions originating in the perinatal period; Q, congenital malformations, deformations, and chromosomal abnormalities. There were 0.87 expected cases of death for the sum of these ICD-10 categories.

[a] Number of deaths after that the underlying cause of death from benign neoplasm (ICD-10 codes: D00–D48) has been recoded for 9 cases to one of the contributing causes. See *Patients and Methods*.
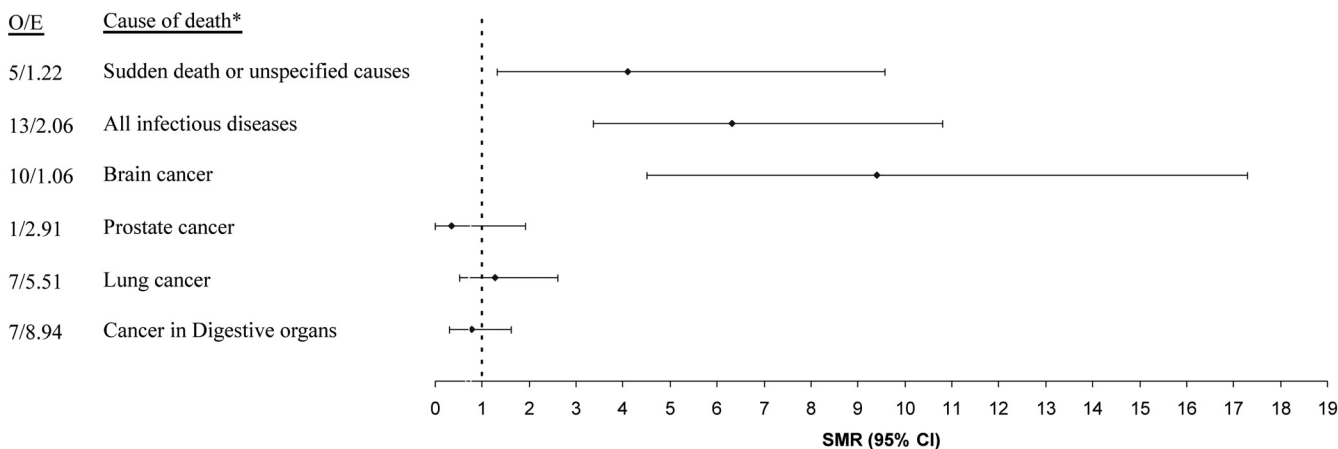
Figure 2. Cause-specific mortality for 1286 hypopituitary Swedish patients compared with the Swedish general population. The SMR (closed circles) and associated 95% CI were plotted for each cause of death. The observed (O) and expected (E) numbers of deaths for each cause of death are also shown. *Sudden death or unspecified causes: ICD-10: R96, R99. All infectious diseases ICD-10 codes: A08–09, A40–41, A46, A 48–49, B 99, J00–J22, G00–G09, K52. Brain cancer ICD-10: C70–C72. Prostate cancer ICD-10: C61. Lung cancer ICD-10: C34. Cancer in digestive organs: C15–C26. Breast cancer: C50. Note: There were no deaths from breast cancer vs an expected 1.84 deaths.

rhythmia according to combined clinical assessment and autopsy findings, and in 1 case, autopsy failed to reveal a specific cause. The remaining patient died in hospital from multiorgan failure.

In summary, increased SMRs were determined for deaths caused by acute infectious diseases, malignant brain tumors, and "other ill-defined/unknown causes of death," whereas death from malignancies in total was not overrepresented (Figure 2).

Infectious diseases and ACTH deficiency/hypocortisolism

ACTH deficiency was present in 58.7% of the total cohort. All 13 subjects who according to the CDR had an infection as the main cause of death were ACTH-deficient. SMR for "All infectious diseases" for ACTH-deficient patients was 8.88 (CI 4.72–15.2) vs 0 (CI 0–6.17) for ACTH-sufficient patients. An acute onset of vomiting, diarrhea, and/or fever/respiratory symptoms preceding circulatory collapse indicated hypocortisolism during intercurrent infectious disease as a main contributor. In total, adrenal crisis likely contributed to death in 8 of the 15 cases with an infectious etiology (Table 3). Seven of these 8 subjects were either found dead at home or died upon arrival to hospital.

Malignant brain tumors

Ten patients died from brain tumors vs an expected number of 1.06 (SMR 9.40, CI 4.50–17.29). Two of the patients had tumor recurrence, while 8 cases, 6 with originally benign pituitary tumors, had de novo malignant brain tumors (Table 4). Six of the 8 patients with de novo malignant tumors had received radiotherapy against the primary tumor 6 to 34 years earlier. All de novo tumors

appeared within the field of radiotherapy. In the group of patients with benign intracranial lesions (pituitary adenoma, craniopharyngioma, n = 277), 1.44% (4/277) treated with radiotherapy before KIMS entry developed a malignant brain tumor, as compared with 0.43% (2/469) of patients treated with surgery alone.

Etiology of hypopituitarism and all-cause mortality

The patients with hypopituitarism following treatment of malignant brain tumors (n = 103) or hematological malignancies (n = 23) had an increased mortality (see Supplemental Table 1, published on The Endocrine Society's Journals Online web site at http://jcem.endojournals.org), SMRs 5.90 and 29.4, respectively. Among those treated for malignant brain tumors, there were 9 deaths. Two died from tumor recurrence, 2 died from de novo brain tumors, 1 died from liver cancer, and 4 died from infectious diseases. In the second category, there were 2 deaths: after cardiac transplantation due to cardiotoxic chemotherapy for acute lymphoblastic leukemia, and intoxication of unknown intent, respectively.

Treatment for pituitary tumors and all-cause mortality

The etiology of hypopituitarism in 794 patients was a benign intracranial tumor (Table 1). Of these patients, 746 had available information on tumor treatment. Of the 746, 611 had a pituitary adenoma. They were treated with surgery alone in 59%, in combination with radiotherapy in 28%, radiotherapy alone in 8%, and other treatments in 5%. The corresponding figures for the 138 cases with craniopharyngeoma were 59%, 28%, 12%, and 1%, respectively.

Transcranial surgery alone (n = 139) or in combination with radiotherapy (n = 109) was associated with higher

Table 3. Hypocortisolism as a Main Cause/Contributor to Death Based on Clinical Presentation Before Death and Autopsy Findings (n = 8)

Sex/ Age at Death	Marital Status	Hormone Replacement	Place of Death	Symptoms Preceding Death (charts)	Underlying Cause of Death: Death Certificate	Contributing Causes of Death: Death Certificate	Cause of Death: Investigator SAE Report/Medical Charts	Cause of Death/Main Findings at Autopsy
M 22	Single	HC, L, T, GH	Home, found dead	Diarrhea and vomiting for a few days	Hypopituitarism	Other specified general symptoms and signs	Possibly gastrointestinal infection with vomiting resulting in inadequate substitution with hydrocortisone and hypoglycemia. The patient had a history of hypoglycemia	Hypopituitarism (low glucose, high lactate in eye fluid) in combination with other acute disease (malaise and vomiting)
M 30	Single/personal assistant daytime	HC, L, T, GH, D	At arrival in hospital	Night before death, diarrhea, vomiting. Felt ill in the morning; contacted father	Craniopharyngeoma	Heart failure, unspecified hypopituitarism	Sudden death, cause unknown. At hospital arrival lethargic, respiratory failure, and asystole. Patient had mild mental retardation	Cause not identified. Cardiac hypertrophy/ dilatation. Coronary arteries intact
M 33	Single	CA, L, T	Home, found dead	Malaise and vomiting	Gastroenteritis	Septicemia unspecified	Hypocortisolism likely to have influenced outcome	Severe gastroenteritis probably infectious, agent not identified
M 43	Singel	HC, L, T, GH, D	In hospital	Sore throat, problems swallowing, fever 1 wk	Acute epiglottitis	Pneumonia, Hypopituitarism	Acute epiglottitis. Initially improved after single oral dose of betametasone. Found dead in bed 1.5 d later preceded by low BP and s-Na. No intravenous hydrocortisone administered. Unkown if oral hydrocortisone de facto was taken	Bilateral pneumonia, somewhat swollen epiglottis
F 53	Married	HC, L, DHEA, GH, D	In hospital, cardiac arrest at arrival	Nausea and vomiting for 24 h. Previously had several Addison crises	Pituitary adenoma	Hypopituitarism, gastroenteritis	Gastroenteritis, hypocortisolism	Pulmonary stasis and edema, no myocardial infarct, mild artheriosclerosis
F 57	Married	HC, L, DHEA, GH	In hospital, shortly after arrival	Intense diarrhea and vomiting for 8 h	Arteriosclerotic heart disease	Brain edema	Gastroenteritis (calici infection verified), hypocortsolism. At arrival to hospital, hypotension, hyperkalemia, circulatory collapse	Brain edema, myocardial hypertrophy, interstitial myocardial fibrosis, calici virus in feces
F 68	Widow	HC, L, GH	Home, found dead	Severe flu last days, swollen leg, weight loss. Daughther suspected noncompliance with medications lately	Pulmonary embolism	Instantaneous death, other ill-defined cause	Unexpectedly found dead at home	Tracheobronchitis, no pulmonary embolism. Coronary arteries intact
F 72	Married	HC, L, E, DHEA, GH	Home, found dead when emergency team arrived	Gastroenteritis for 24 h, contacted medical staff, recommended to drink water and stay at home	Gastroenteritis	Shock unspecified, Dehydration	Gastroenteritis, Addison crisis	Autopsy not performed

Abbreviations: CA, cortisone acetate; D, desmopressin; E, estrogen; HC, hydrocortisone; L, levothyroxine; SAE, serious adverse event; T, testosterone.

Table 4. Death Caused by De Novo Malignant Brain Tumors (n = 8)

	Cause of Death	Sex/Age at Death	Onset of GHD	Etiology of Hypopituitarism	Treatment of Initial Tumor	Radiotherapy Total Dose (Gy)	Years Between Radiotherapy and De Novo Tumor
1.	Anaplastic astrocytoma[a]	F 23	CO	Medulloblastoma[a]	S, Rx chemotherapy	35 CNS total 55 occipital region	11
2.	Malignant glioma[b]	M 31	CO	Germinoma[b]	S, Rx	35 spinal region 50 suprasellar region	15
3.	Oligodendroglioma	F 35	AO	Pit. adenoma; NF	S, Rx	46	6
4.	Glioblastoma multiforme	M 61	CO	Craniopharyngeoma/ cholesteatoma	S	—	51 (after S.)
5.	Astrocytoma	M 63	AO	Pit. adenoma; NF	S, Rx	40	7
6.	Glioblastoma multiforme	F 65	AO	Pit. adenoma; GH secreting	S, Rx	40	33
7.	Astrocytoma, brain stem	M 71	AO	Pit. adenoma; NF	S	—	4 (after S.)
8.	Glioblastoma multiforme	F 74	AO	Craniopharyngeoma	Rx	Isotope instillation, yttrium implantation, stereotactic gammalesion	32–34

Abbreviations: AO, adult onset; CO, childhood onset; NF, nonfunctioning; Pit., pituitary; Rx, radiotherapy; S, surgery. External fractionated radiotherapy (conventional) was given in cases 1, 2, 3, 5, and 6.

[a] Location of the anaplastic astrocytoma, parieto-occipal region. Location of the medulloblastoma, occipital region.

[b] Location of the malignant glioma, right thalamus. Location of the germinoma, suprasellar.

mortality rates with SMR of 2.56 (CI 1.60–3.87; deaths observed n = 22 vs expected n = 6) and 1.67 (CI 0.93–2.75; deaths observed n = 15 vs expected n = 9), respectively. SMRs for radiation therapy alone (n = 66), or in combination with transphenoidal surgery (n = 97), or from transphenoidal surgery alone (n = 293), were not significantly different from general population rates. After adjustment for attained age, sex, and etiology, there was no significant heterogeneity in SMR between types of treatment (P = .45). One explanation for this nonsignificant observation is the association between type of treatment and etiology of hypopituitarism.

SMR for stroke after transcranial surgery was 4.80 based on 3 observed and 0.63 expected cases (CI 0.96–14.0), after treatment with transcranial surgery and radiotherapy 3.30 based on 2 observed and 0.87 expected cases (CI 0.37–11.90), and after transphenoidal surgery 1.02 (CI 0.11–3.68) based on 2 observed and 1.96 expected number of cases.

Pituitary hormone deficiencies and all-cause mortality

The SMR in ADH (antidiuretic hormone)-deficient patients was 2.79 (CI 1.95–3.86). With adjustment for attained age, gender, and etiology, SMR was 2.17 times higher in ADH-deficient patients compared to ADH-sufficient patients (CI 1.46–3.23, P = .0001). SMR in ACTH-deficient patients was 1.53 (CI 1.23–1.88) and in ACTH-sufficient patients was 1.18 (CI 0.80–1.68) (P = .11). Similarly, no significant differences were found with respect to TSH status and FSH/LH status, respectively.

A history of prior treatment with GH at KIMS entry and treatment duration in KIMS did not significantly influence variation in mortality rates (data not shown). When controlled for age and gender, the average IGF-I SDS over the treatment period was −0.07 for deceased patients vs 0.12 for patients alive at the end of follow-up. The difference between dead and alive patients, −0.19 (CI −042–0.05), was not significant (P = .12).

Discussion

This comprehensive study confirms and extends findings of an increased mortality in patients with pituitary insufficiency including GHD, in particular, in younger patients (1). In contrast to the previous investigations, this was not accounted for by an excess cardiovascular or cerebrovascular mortality, or by a recurrence of malignant tumors; instead, new findings with implications for management of the patients were made.

There were 15 deaths in infections, all in ACTH-deficient patients. The type of infections ranged from life-threatening sepsis and epiglottitis to generally benign conditions like gastroenteritis. Overall, hypocortisolism was likely to be the main or a major contributing cause of death in 6.7% (8/120) of all deaths, a percentage rising to 25% (4 of 16) of the deaths occurring before the age of 45. Most (7/8 = 87.5%) of these patients had a sudden death and were either found dead at home or died shortly after arrival to the emergency unit. For the 5/8 patients (62.5%) who were living alone, relatives and/or friends had pro-

vided information of an acute episode of vomiting and diarrhea shortly preceding the death. Postmortem examinations did not offer alternative explanations for the sudden unexpected deaths. It is conceivable that failure to adjust the glucocorticoid dose, and/or to administer glucocorticoids parentally during episodes of vomiting had led to the fatal outcome.

In a survey of the prevalence of adrenal crisis in patients with adrenal failure, a substantial proportion had experienced at least 1 crisis: 46% in primary adrenal failure, 35% in secondary adrenal failure (13). In patients with autoimmune adrenal failure, the mortality rate was increased in subjects below the age of 40, in particular, in young men (14). In this subgroup, acute adrenal failure was the major cause of premature death. An association between mortality and secondary adrenal insufficiency has been observed in children (15, 16). In the study of Taback et al (15), 1366 children treated with GH during 1967–1985 were followed up in 1992. Of the 37 deceased patients, 9 had died from an adrenal crisis or hypoglycemia. In the study by Mills et al (16) of more than 6000 young adults who had received pituitary-derived GH as children, 70% had multiple pituitary hormone deficiencies. At follow-up 433 had died vs 114 expected. Deaths were sudden in 25%, and adrenal insufficiency-related in more than half of these cases. A third of the deaths were associated with infections. Our study strongly indicates that also in adult hypopituitary patients inadequate treatment of hypocortisolism during major stressful events remains a significant cause of death.

The other major finding in this study was that 8 patients had died from a de novo malignant brain tumor, in 6 cases after a latency period of 6 to 34 years postradiotherapy. Three of the deaths occurred in patients less than the age of 40 years. All tumors were confirmed by histology. None of the diseased patients had a family history of CNS tumors.

Cranial irradiation for acute lymphoblastic leukemia (17), and for benign intracranial tumors (18) including pituitary tumors (19–21), has been associated with an increased risk of developing a de novo brain tumor. An increased incidence of meningeomas after low-dose irradiation for tinea capitis (22) and no findings of second brain tumors in cohorts of nonirradiated pituitary adenoma patients (21) likewise indicate irradiation as a causative agent. In cohorts treated with surgery and fractionated radiotherapy therapy for benign pituitary adenomas, the relative risk for a second brain tumor, a benign meningeoma and/or a malignant tumor, was calculated to be 5.2 to 16 times above that of the reference population, with a cumulative risk of 1.3% to 1.7% at 10 years, 1.3% to 2.4% at 15 to 20 years, and 4.8% at 30 years of follow-up (21).

The true incidence of all de novo CNS tumors in our cohort (ie, both benign and malignant) is unknown because the scope of the study was to assess causes of death. Given that benign meningeomas have constituted one-half to two-thirds of the new brain tumors observed after cranial irradiation, our findings reveal a higher excessive risk for developing a malignant brain tumor than previously recognized. A longer average period since radiation therapy, 24.8 vs 7.9–14 years in previous studies, may account for the difference. In studies from the mid 1990s, malignant de novo tumors typically appeared within a 10-year period after irradiation, whereas benign meningeomas presented later. In recent studies with longer periods of follow-up, de novo malignant tumors appeared also after 20 to 30 years (21, 23). Collectively, the present and previous data translate into 1 to 2 deaths from de novo malignant brain tumors over a 20- to 30-year period in 100 patients treated with radiotherapy for benign pituitary adenomas.

The finding of 2 de novo malignant brain tumors in pituitary adenoma patients not exposed to radiotherapy warrants further investigations. One study has suggested pituitary adenomas to be associated with an increased risk of another tumor, but brain tumors were not among the reported ones (24). Recently, repeat CT scans delivering a cumulative dose of about 60 mGy in children were found to triple the risk of brain cancer (25).

In contrast to previous studies, cardiovascular or cerebrovascular mortality did not significantly exceed that of the reference population. Most previous studies have investigated deaths that occurred before 1987–1994 (2, 3, 5, 9), or before 2000–2001 (4, 10). In the present study deaths occurred later, 1995–2009, thus reflecting a cohort of patients subjected to a more contemporary regimen of medical care. During the last 10 to 15 years, there has been a more active approach to cardiovascular risk factors in general, and regarding pituitary tumor patients, a refinement of surgical procedures, less use of radiotherapy, and improved hormone replacement regimens. Besides the introduction of GH replacement in adults, the glucocorticoid replacement doses have been lowered, influenced by the finding of lower cortisol production rates in healthy subjects than previously assumed (26). In support of a clinical relevance of lowered hydrocortisone replacement doses in hypopituitarism is the association between daily doses above 20 mg and a worsened cardiovascular risk profile (27), and a relation between hydrocortisone doses and cardiovascular mortality in acromegaly (28). Further, as a consequence of the report of an association between cardiovascular morbidity and the use of combined sex hormones (29), fewer women of postmenopausal age now receive peroral sex steroids. It is of note that in two recent

studies of hypopituitary patients, cardiovascular mortality was not above the expected (7, 11), but cerebrovascular remained modestly elevated in one study (11), and in women only in the other (7).

There are a number of methodological strengths with this study. Since 1961, the death of every subject in Sweden generates a report to the CDR. Information includes the date and venue of death, the underlying cause, and contributing diseases/conditions. In the global KIMS study on mortality (11), the cause of death was reported to the KIMS investigator.

Subsequently, this event was coded according to the World Health Organization Global Burden of Disease categories by the authors themselves, thereby introducing a potential coding bias. In the present study the coding procedure in the deceased patients and the comparator population was identical, and temporal changes in mortality over time were accounted for. Another strength is that medical charts and autopsy reports were reviewed. This enabled the conclusions regarding adrenal crisis to be made. Furthermore, the observation that most deaths from brain tumors was not, as might have been anticipated, attributed to tumor recurrence, would otherwise have remained unrecognized.

The current study design is associated with a potential selection bias because patients enrolled in the database were eligible for treatment with GH and may have more or less severe pituitary insufficiency and comorbid conditions. Acute critical illness and active malignancy are both contraindications for GH treatment. It is conceivable that subjects with a previous history of malignancy also are excluded, at least for some years following cancer therapy. A tendency of fewer than expected deaths in cancer of the prostate and breast would support this speculation. In addition, a close follow-up of patients in a register may be associated with improved patient care.

In summary, we found a significant proportion of possibly preventable deaths, ie, inadequately treated hypocortisolism during stress. This highlights a need for increased awareness of patients, their relatives, and health personnel and calls for making available user-friendly emergency kits for parenteral injection of hydrocortisone. Furthermore, the increased risk of developing a malignant brain tumor after radiotherapy implicates a need for long-term surveillance and calls for restrictive use of this treatment modality, in particular, in younger patients, and in cases where alternative therapy is an option.

Acknowledgments

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