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Update in Mortality in GH-Treated Patients

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During GH therapy for 2.3–9.6 years, male adult-onset GH-deficient patients with a diagnosis of a nonfunctioning adenoma have no increased all-cause mortality. However, women with adult-onset GH deficiency (GHD) are still at slightly higher risk. This general improvement in mortality is due to a more contemporary regimen of cardiovascular drugs, a refinement of surgical procedures, besides the introduction of GH therapy improved hormone replacement regimens with lowered glucocorticoid replacement, updated approaches of sex steroids for women, and less use of cranial radiotherapy. The underlying disease is the most important predictor for mortality: eg, a craniopharyngioma, malignant causes of hypopituitarism, previous Cushing's disease, and the presence of diabetes insipidus/aggressive tumors. The main cause of increased mortality was cerebrovascular diseases and infectious/respiratory diseases in ACTH-deficient patients. Furthermore, there was a significant impact of young age at disease onset and of death from secondary brain tumors, with a higher risk after cranial radiotherapy.

Reports on four cohorts of GH-treated childhood-onset GHD patients have been published. Two of them included only patients with idiopathic isolated GHD, neurosecretory dysfunction, idiopathic short stature, or being born short for gestational age. Increased mortality in circulatory disorders, ill-defined diseases, and bone cancer were recorded in one study, but not in the other smaller study, where suicide and accidents caused the majority of deaths. A third childhood-onset GHD cohort included patients with a background of malignant tumors, craniopharyngioma, pituitary adenomas, pituitary aplasia/hypoplasia, and trauma. An increase of all-cause mortality was recorded in both males and females. The fourth cohort included isolated GHD and idiopathic short stature (60%), but also diagnosis of chronic renal failure and Turner's syndrome. In these latter studies, an underlying serious condition was the most important factor for death, with central nervous system tumors (recurrent or new tumor) being the leading cause of mortality. (***J Clin Endocrinol Metab*** 98: 4219–4226, 2013)

More than 20 years ago, three studies (1–3) showed increased mortality in cardiovascular disease (CVD) and particularly cerebrovascular diseases (2, 3) in patients with conventionally treated hypopituitarism, but without GH therapy. These studies included patients with operated nonsecreting pituitary adenomas and craniopharyngiomas but excluded patients with acromegaly and Cushing's disease. The suggested reasons for the increased CVD mortality were, eg, GH deficiency (GHD) (1, 2), unsubstituted or inadequately substituted deficiencies of other pituitary hormones, cranial radiotherapy (CRT) (2), and in women, unsubstituted sex steroids (3). For a long time we have awaited a prospective surveillance study of a large cohort of conventionally substituted GHD patients, with and without GH therapy. However, the recombinant human GH (rhGH) widely used since 1995 has made such an effort difficult. In addition, such a study is a real challenge because an adjustment has to be made for imbalances in patients' characteristics between GH-treated and untreated groups (4). In recent years, studies of nonmatched cohorts of GH therapy have been published, and comparisons have been made to a general or a global population. This update on the mortality of GH-treated patients will focus on the publications from the last 3 years. Both adult-onset (AO) and childhood-onset (CO) GHD will be discussed. However, the study populations are not completely comparable between CO and AO

Abbreviations: ADH, antidiuretic hormone; AO, adult onset; CDR, cause of death registry; CI, confidence interval; CNS, central nervous system; CO, childhood onset; CRI, chronic renal insufficiency; CRT, cranial radiotherapy; CVD, cardiovascular disease; GHD, GH deficiency; HR, hazard ratio; IGHD, isolated GHD; ISS, idiopathic short stature; PMS, postmarketing surveillance; rhGH, recombinant human GH; RR, relative risk; SGA, short for gestational age; SMR, standardized mortality ratio; TS, Turner's syndrome.

Table 1. Cohort Characteristics and Background Entities That Impact on Mortality in Cohorts With a Majority of AO GHD on GH Therapy

First Author, Year (Ref.)	PMS Study (Yes or No)/ Dates on GH Therapy	Mean Duration of GH Therapy, y	Cohort Size/ Person-Years of GH Therapy, n	AO GHD vs CO GHD, %	Background Diagnosis
van Bunderen, 2011 (7)	No/Dutch National Registry 1985–2009	5.7	2229/13 353	77.1/22.9	[a]Other, 40.1%; NFA, 29.8%; [b]secreting adenoma, 9.8%; CP, 11.2%; malignant causes, 9%
Gaillard, 2012 (8)	Yes/NA	4.9	13 983/69 056	77/23	NFA, 38%; secreting adenoma, 8%; pituitary atrophy, 18%; CP, 11%; benign tumor/lesions, 3%; aggressive tumors, 8%; [c]miscellaneous etiology, 14%
Burman, 2013 (9)	Yes/1995–2009	9.6	1286/11 450	71/29	Idiopathic/congenital, 18.3%; CP, 10.7%; NFA and PRL, 40.7%; secreting adenomas, 7.2%; malignant brain tumors, 8%
Hartman, 2013 (4)	Yes/1996–2002	2.2	1988/4655	84/16	Intracranial tumors, 63%

Abbreviations: NA, not applicable; NFA, nonfunctioning adenoma; CP, craniopharyngioma; NP, national population; GP, global population; PRL, prolactinoma.

[a] "Other" includes Sheehan's syndrome, congenital or idiopathic GHD.

[b] Secreting adenoma, GH and ACTH.

[c] Miscellaneous etiology, eg, traumatic brain injury.

GHD patients. In addition, the AO GHD population also includes a portion of the CO GHD population. Two of the cohorts with CO GHD had a completely different background diagnosis compared to the AO GHD population, with idiopathic isolated GHD (IGHD) neurosecretory dysfunction, idiopathic short stature (ISS), or being born short for gestational age (SGA) (5, 6).

Cohorts of National Patient Registries and Post-Marketing Surveillance (PMS) Studies of GHD Patients

Cohorts with a majority of AO GHD (Table 1)

van Bunderen et al (7) analyzed retrospectively and anonymously the Dutch National Registry of Growth Hormone Treatment in Adults. Up to 2009, a total of 2229 patients were treated with GH.

Gaillard et al (8) studied the KIMS (Pfizer International Metabolic Database), which evaluates data from all hypopituitary patients, with the exception of those with idiopathic isolated AO GHD. The total KIMS study cohort included 13 983 patients.

The Swedish KIMS database (9) contained information on patients with CO or AO GHD who were treated with Genotropin. Included were 1335 patients, and full identity was provided for 1286 patients.

The US Hypopituitary Control and Complication Study (HypoCCS) (4) was a prospective PMS study sponsored by Eli Lilly and Company to examine the long-term safety of Humatrope treatment in adults with GHD. Be-

Table 2. Cohort Characteristics and Mortality After rhGH Therapy in National Registries or PMS Studies of CO GHD Patients

First Author, Year (Ref.)	Mean Duration of GH Therapy, y	Years at Start of GH Treatment or at GHD Diagnosis	Census Date/Mean Age of Patients Living at End of Follow-up, y	Vital Status of the Total Cohort, %
Bell, 2010 (10)	Not mentioned	1985–2006	January 2006/NA	NA
Stochholm, 2012 (11)	NA/76% GH treated	GHD diagnosis, 1970–1999	December 2008/NA	NA
Carel, 2012 (5)	3.9 ± 2.6	1985–1996	September 2009/ 28.3	94.7
Sävendahl, 2012 (6)	Not mentioned	1985–1997	December 2010/28.3 (S), 29.4 (B), 27.2 (TN)	98.4 (S), 97 (B), 97.8 (TN)

Abbreviations: NA, not applicable; S, Sweden; B, Belgium; TN, The Netherlands; CP, craniopharyngioma; PWS, Prader Willis syndrome; NP, national population.

[a] IGHD refers to otherwise healthy children who have low stimulated GH levels with normal magnetic resonance imaging scans and no other reason for GHD,

[b] ISS refers to short, otherwise healthy children distinguished from IGHD only by higher GH testing results.

[c] Other conditions associated with growth failure (Prader Willis syndrome).

[d] Other, by far the largest, and consisted mainly of benign tumors, including pituitary adenomas, aplasia/hypoplasia of the pituitary, and trauma.

Table 1. Continued

Same CDR Retrieval in Patients Cohort as in National Registries	Overall Mortality, SMR (95% CI)	Higher Mortality in Females vs Males/Young Age at Disease Onset	Increased Mortality in Cerebrovascular Disease/SMR (95% CI)	Increased Mortality in Infectious Disease	Increased Mortality in CP
Yes	NP, 1.27 (1.04–1.56)	Yes/yes	Yes/2.54 (1.41–4.59)	No	Yes
No	GP, 1.13 (1.04–1.24)	Yes/yes	Yes/1.88 (1.44–2.41)	Yes	Yes
Yes	NP, 1.42 (1.18–1.70)	Yes/yes	No	Yes	NA
No	NP, 0.86 (0.59–1.21)	No/no	No	No	No

tween 1996 and 2002, data were verified against source documents by monitors reviewing patient records at the sites. The 2430 subjects (1988 GH-treated and 442 untreated) who enrolled in US HypoCCS were the focus of this report.

Details of study type and dates, duration on GH therapy, cohort size/person years of treatment, percentage of AO GHD vs CO GHD, background diagnosis of GHD, cause of death retrieval, overall mortality, and background entities that had an impact on mortality are shown in Table 1.

Cohorts of CO GHD (Table 2)

Between 1985 and 2006, the National Cooperative Growth Study (NCGS), a multicenter PMS study initiated by Genentech Inc, monitored the safety and efficacy of

rhGH in 54 996 children (65% males) in North America (10).

Stochholm et al (11) performed a study on the Danish Nationwide Registry. A total of 260 GH-deficient males and 156 GH-deficient females were included. However, only 76% were GH treated.

Carel et al (5) used the mandatory French population-based register of all patients (n = 6928) who were treated with GH in France until 1996 and were born before January 1, 1990 (the Safety and Appropriateness of Growth Hormone Treatments in Europe, SAGhE). Characteristics of the patients were obtained from pediatric endocrinologists until 1996 when the national compulsory France-Hypophyse register was disbanded. Additional follow-up data on GH treatment were collected from clinical centers

Table 2. Continued

Cohort Size/ Person-Years of Follow-up	Background Diagnosis	Overall Mortality, HR or SMR (95% CI)	Causes of Death	Same Cause of Death Retrieval in Patients Cohort as in National/Regional Databases
54 996/195 419	[a]IGHD, 42.5%; OGHD, 15.2%; TS, 9.3%; CRI, 3.2%; [b]ISS, 17.8%; [c]other, 11.9%	NA	174 deaths, CNS tumors (recurrence or new onset). Sudden death: TS = aortic dissection; PWS = respiratory failure, adrenal crises	NA
416/NA	Malignant tumors, CP, IGHD, [d]other	Adjusted HR: males, 5.2 (3.5–7.6); females, 10.5 (5.7–19.1)	32 patients died from cancer, of which 30 (94%) were related to CNS	Yes
6928/116 403	IGHD (n = 5162), neurosecretory dysfunction (n = 534), ISS (n = 871), SGA (n = 335)	NP: SMR, 1.33 (1.08–1.64)	Circulatory diseases/ill-defined diseases/bone cancer	Yes
2543/46 556	IGHD (n = 1666), ISS (n = 552), and SGA (n = 325), without syndrome or genetic defects	NA	Of 21 deaths, 12 from accidents, 4 from suicide	NA

in 2008–2010. The mean follow-up time from treatment initiation to death or loss to follow-up or census was 17.3 ± 4.1 years. Patients receiving mean GH doses greater than 50 μg/kg · d were treated for 3.5 ± 1.9 years with a mean dose of 70.1 ± 17.2 μg/kg · d.

Sävendahl et al (6) studied patients on rhGH treatment during childhood, irrespective of treatment duration, who had attained 18 years of age by the end of 2009 (The Netherlands) or the end of 2010 (Belgium and Sweden). National registries in Belgium, The Netherlands, and Sweden were used for the identification of patients.

Details of years on GH therapy, year of patient inclusion, census date, vital status, cohort size/person-years of treatment, background diagnosis, overall mortality, causes of death and retrieval are shown in Table 2.

Cohort Comparisons, Cause of Death Ascertainments, and Loss of Ascertainment of Deaths

Cohorts with a majority of AO GHD (Table 1)

In the Dutch cohort, date and cause of death were collected through medical records and death certification from the Dutch Central Bureau of Statistics (7). CVD was defined as International Classification of Disease, 10th Revision (ICD-10), codes I20–I79 (including cerebrovascular accidents, I60–I69). In 22 patients (16%), cause of death could not be recovered.

The global KIMS study protocol required the physician's report of all death events (8). Comparisons were made between the patient's cohort and cause of death according to the World Health Organization Global Burden of Disease cause categories (the global) (12). Eighty of the 528 (15%) deceased were not identified.

From KIMS Sweden, the comparison on causes of death was based on the diagnoses in the cause of death registry (CDR), which uses the ICD-10 (9). A total of 120 patients had died. A composite endpoint of "all infectious diseases" was made of the following CDR ICD-10 codes: A08–A09, A40–A41, A46, A48–49, B99, J00–J22, G00–G09, and K52.

In the HypoCCs, causes of death were reported as defined by regulatory criteria (4). To ensure accuracy, investigators were contacted for follow-up information on all deaths. Standardized mortality ratios (SMRs) were used to quantify the risk of death among the GH-treated and untreated groups. An expected number of deaths were calculated using age- and sex-specific US mortality rates reported by the National Center for Health Statistics.

Cohorts of CO GHD (Table 2)

In the NCGS, treatment with rhGH is as prescribed by the individual physician. Events were reviewed by the Genentech Drug Safety scientist (10).

Stochholm et al (11) used only the primary cause of death and the ICD-10 for analyses of cause-specific mortality. Hazard ratios (HRs) were calculated for all-cause mortality. Controls from the general population were matched for age (same year of birth) and gender. By this procedure, 25 352 male and 15 110 female controls were identified.

Carel et al (5) calculated the risk of death by the SMR with adjustment for year, age, and sex using the French general population as the reference group. The cause of death, as indicated in death certificates, was obtained from the French Centre of Epidemiology on Medical Causes of Death and coded according to the revision of the ICD effective at the time of death and further bridge coded to the ninth revision.

Sävendahl et al (6) obtained vital status data from the National Population Registry from each country. The cause of death was retrieved from a national CDR in Sweden, from the federal and the three regional death registries in Belgium, and from individual patient records in The Netherlands (n = 484).

Overall Mortality and the Impact of Background Diagnosis, Treatment of Primary Disease, Age at Disease Onset, and Antidiuretic Hormone (ADH) and ACTH Deficiency on Mortality After GH Therapy

Cohorts with a majority of AO GHD (Table 1)

In the Dutch study (7), 95 patients in the treatment group had died, compared to 74.6 expected (SMR, 1.27; 95% confidence interval [CI], 1.04–1.56). Mortality was increased in women but not in men. After exclusion of high-risk patients (craniopharyngiomas, malignant causes of hypopituitarism), the SMR for CVD mortality remained increased in women. Patients with an underlying diagnosis of craniopharyngioma or other possible malignant cause of hypopituitarism did very poorly. Increased SMR was observed in patients who underwent transcranial surgery and/or radiotherapy of the primary tumor. Patients with CO GHD had increased mortality, compared to the AO GHD patients.

Gaillard et al (8) recorded 528 observed deaths vs 465.5 expected deaths with an SMR of 1.13 (95% CI, 1.04–1.24). Mortality in female patients was significantly higher (SMR, 1.56; 95% CI, 1.36–1.78), but mortality in

male patients was within the expected range (SMR, 0.94; 95% CI, 0.84–1.06). Significantly elevated SMR was seen in patients with Cushing's disease, craniopharyngiomas, aggressive tumors, and diabetes insipidus. For all etiological categories, SMR remained inversely associated with attained age and was increased in females. SMR in the group of CO patients was 2.92 (95% CI, 2.25–3.72), and in the group of AO patients, SMR was 1.04 (95% CI, 0.95–1.14).

In the Swedish KIMS, the observed number of deaths was higher than the expected, 120 vs 84.3 (SMR, 1.42; 95% CI, 1.18–1.70) (9). SMR was 1.63 (95% CI, 1.18–2.18) in women vs 1.33 (95% CI, 1.05–1.66) in men (P = .34). In patients with a benign pituitary tumor including craniopharyngioma (n = 794), the SMR was 1.35 (95% CI, 1.08–1.65), but the mortality was only increased in females (SMR, 1.56; 95% CI, 1.08–2.18), not in males (SMR, 1.25; 95% CI, 0.95–1.61) (A. Mattsson, personal communication). SMR in ADH-deficient patients was 2.79 (95% CI, 1.95–3.86). SMR for ACTH-deficient patients was 1.53 (95% CI, 1.23–1.88), and in ACTH-sufficient patients, SMR was 1.18 (95% CI, 0.80–1.68). Transcranial surgery alone (n = 139) or in combination with radiotherapy (n = 109) was associated with higher mortality rates, with SMRs of 2.56 (95% CI, 1.60–3.87) and 1.67 (95% CI, 0.93–2.75), respectively. SMR for CO GHD was 2.25 times higher than for AO GHD.

In HypoCCs, the all-cause SMR was not increased in either GH-treated (0.86; 95% CI, 0.59–1.21) or untreated (0.58; 95% CI, 0.29–1.04) groups and did not differ significantly between GH-treated and untreated patients, respectively (P = .26) (4).

Cohorts of CO GHD (Table 2)

In the Danish study, mortality was increased (male HR, 10.7; female HR, 21.4), and after adjustment for marital and educational status, male HR of death was 5.2 and female HR was 10.5 (11).

In the study of Carel et al (5), 93 of the 6928 patients died during follow-up. All-cause mortality was significantly higher, with an SMR of 1.33 (95% CI, 1.08–1.64). Increased mortality would not have been detected if duration of follow-up had been limited to 5 or 10 years after the end of treatment. Those who received higher mean doses of GH or were shorter at the start of treatment had significantly higher mortality rates (P for trend <.04 and P < .05, respectively). Poisson regression analysis showed that the highest treatment dose category was still significantly associated with mortality after adjustment for height SD score at the start of treatment.

Sävendahl et al (6) showed that of 2543 patients, 21 (4 females and 17 males) had died. In deceased subjects, the duration of GH treatment varied from 0.4–12.8 years, and the mean GH dose varied from 0.027–0.054 mg/kg · d. Due to low statistical power, no risk estimate with SMR was provided.

Specific Causes of Death After GH Therapy: CVD, Malignancies, Infectious Disease, and Presence of ACTH Deficiency

Cohorts with a majority of AO GHD (Table 1)

In the Dutch study, the SMR for CVD was more than 2-fold increased in women but was not increased in men (7). Exclusion of patients with former GH- or ACTH-secreting adenoma did not significantly change the results. After exclusion of high-risk patients (craniopharyngiomas, malignant causes of hypopituitarism), the overall SMR due to malignancy was significantly lower than the general population. In the GH treatment group, the overall SMR for death due to cerebrovascular accidents was 2.54 (95% CI, 1.41–4.59), the SMR for men was 1.97 (95% CI, 0.82–4.73), and the SMR for women was 3.37 (95% CI, 1.51–7.50).

Although CVD and malignancy were the leading causes of death in the Global KIMS cohort, the overall SMR for these cause categories was not significantly increased (8). Two other frequent causes of death, cerebrovascular disease (irrespective of primary radiotherapy) and infectious diseases, were associated with a significantly increased SMR. Of the 86 patients whose deaths were due to infectious diseases, 71 (82.6%) had ACTH deficiency and were receiving glucocorticoid replacement therapy. Furthermore, the risk of death from infectious diseases was 1.6-fold higher in patients with ACTH deficiency than in patients without ACTH deficiency (95% CI, 0.9–2.8; P = .088).

In the Swedish KIMS, the cause of death was significantly increased for benign neoplasms (n = 5), diseases of the respiratory system (n = 10), diseases of the digestive system (n = 9), and symptoms, signs, and abnormal clinical and laboratory findings not elsewhere classified ("ill-defined," n = 5) (9). The composite endpoint "all infectious diseases" resulted in a calculated SMR of 6.32 (95% CI, 3.36–10.8), and SMR for "all infectious diseases" for ACTH-deficient patients was 8.88 (95% CI, 4.72–15.2) vs 0 (95% CI, 0–6.17) for ACTH-sufficient patients. Furthermore, the SMRs 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. An increased risk of death from brain tumors with an SMR of 9.40 (95% CI, 4.50–17.3) was recorded.

Cohorts of CO GHD (Table 2)

In the NCGS, 174 deaths were reported, 19 (11%) were assessed as related to rhGH by the investigator, four were designated as not assessable, and no causality was provided for 21 (10). Of these 19 deaths, 12 were related to central nervous system (CNS) tumors. The remaining deaths (7 of 19) were all due to primarily isolated cases. A total of 130 deaths (75%) were assessed as unrelated to rhGH by the investigators. Among Turner's syndrome (TS) patients, there were five deaths from aortic dissection/ rupture. No deaths related to this cardiovascular event were reported in any other patient group in the NCGS. In patients with organic GHD (OGHD) and idiopathic pan-hypopituitarism, four deaths were consistent with acute ACTH insufficiency.

In the Danish study, 32 patients died due to cancer, of which 30 (94%) were cancers related to the CNS (11). Of these 32 patients, 78% were CNS irradiated, 28% had pituitary operation, 41% received GH treatment, and 22% had a primary diagnosis of malignant cancer.

In the French study, a significant increase in mortality due to diseases of the circulatory system (SMR, 3.07; 95% CI, 1.40–5.83) or cerebrovascular disease (SMR, 5.29; 95% CI, 1.42–13.55) was recorded (5). Furthermore, mortality in ill-defined conditions was increased, whereas other causes of mortality, including neoplasms in particular, were no more frequent than expected. However, bone tumor-related mortality was increased (SMR, 5.00; 95% CI, 1.01–14.61).

In the study of Sävendahl et al (6), the majority (76%) of deaths were caused by an accident (n = 12) or suicide (n = 4). Due to low statistical power, no risk estimate (SMR) was provided.

Discussion

On GH therapy, both national registries and PMS studies of AO GHD patients, with a majority of patients suffering from nonsecreting adenomas, showed a normal survival in GH-deficient men (7–9). However, the risk in women was still increased, but at a lower level (7–9). This general improvement of mortality is due to a more contemporary regimen of cardiovascular drugs, a refinement of surgical procedures, besides the introduction of GH therapy improved hormone replacement regimens with lowered glucocorticoid replacement, updated approaches of sex steroids for women, and less use of CRT. This is in accordance with a Swedish National study (non-PMS) showing a significantly lower incidence of nonfatal myocardial infarction in men and no increase in the risk of nonfatal stroke in women after 6 years of GH therapy (13).

In this study, men used more antihypertensive drugs, and women used more lipid-lowering drugs. One reason for the increased risk in women might be the significantly longer symptom duration of hypopituitarism in women, compared to men, before the diagnosis of a pituitary tumor (14). Furthermore, the percentage of diagnosed hypopituitarism was shown to be higher in men compared to women in patients with nonsecreting adenomas (15). This means that we seem to underdiagnose hypopituitarism in women both before and after the diagnosis of a pituitary tumor. Based on recent recommendations, unfortunate exposure to estrogens or/and gestagen compounds with both a long and late exposure time can now be avoided (16). The positive metabolic effect of GH therapy cannot, however, be questioned, and early GH replacement can, at least in theory, reduce an evident CVD risk.

Cerebrovascular mortality remained elevated in GH-treated patients in two of the studies (7, 8) (Table 1) and was again more evident in women. The reason is not completely understood, but the underlying diagnosis, as an indication for radiotherapy, is an important factor (7). Experimental data and case reports clearly support the notion that CRT might act as a risk factor for cerebrovascular disease, but available epidemiological studies do not provide clear evidence to implicate CRT as a stronger risk factor than other factors; eg, surgical trauma, unfortunate exposure to sex steroids in women, or unphysiological exposure to other hormones (glucocorticoids) and undiagnosed hypopituitarism (17). The level of relative risk (RR) increase of mortality from CRT was shown in patients with acromegaly, where CRT was associated with a significantly increased RR of mortality (RR 1.8 [1.2–2.8]) and this was also true for ACTH deficiency groups (RR 1.7 [1.2–2.5]) (18). The RR of radiotherapy was comparable to an increase in the dose of hydrocortisone above 20 mg (between 25–30 mg/d) (18).

The current AO GHD PMS studies are associated with potential selection bias because patients enrolled in the database may have less severe pituitary insufficiency and comorbid conditions (4, 8, 9). In addition, in some of the PMS studies, the follow-up was too short to exclude either CVD risk or malignancies. GH replacement therapy in the AO GHD population was not associated with a higher overall SMR from malignancies (9). On the other hand, in the US cohort (PMS study) (4), comparison was also made to a control group of non-GH-treated GHD patients with more comorbidities, but with no difference in malignancies. This is in contrast to cohorts with a previous history of childhood cancer who showed a marked increase in long-term cancer mortality (19).

Of great importance is an increased mortality in infectious diseases (respiratory diseases) (8, 9), already re-

corded by the historical cohorts (2, 3), and in the recent studies this increased mortality was particularly recorded among ACTH-deficient patients (8, 9). In addition, GH therapy may also unmask a state of cortisol/ACTH deficiency, needing timely hydrocortisone substitution (20).

Today the increased mortality risk in AO hypopituitary patients is particularly related to a diagnosis with defined large tumor masses illustrated by the presence of ADH deficiency and of craniopharyngiomas or in patients with other aggressive etiology (7, 8). The consequence of treatment of large pituitary tumors masses on mortality after GH therapy is illustrated by the fact that transcranial surgery alone or in combination with CRT was associated with higher mortality (8, 9). This increased risk is possibly related to hypothalamic involvement by the tumors, causing morbid obesity and increased metabolic risk (21).

Three (5, 6, 11) of the four GH-treated CO GHD cohorts were national registries (Table 2). The strength of national register-based information is that it minimizes the selection problems often found in studies requiring active participation. By far the largest of the studies was from France, the SAGhE study (5). An intense debate and communication has followed; eg, the comparison would not have been to the general population, but to patient groups with ISS and IGHD and those born SGA left without GH therapy and ideally matched for sociodemographic characteristics (22). A weakness of the SAGhE study is, of course, the mixture of follow-up data because from 1985 to 1996 the mandatory register was used, but additional follow-up data on GH treatment were collected from clinical centers in 2008–2010. Furthermore, most of the difference in total deaths was in the category "idiopathic," meaning that no cause of death was stated on the death certificate. Time of follow-up was important because SAGhE only found a long-term effect after 15–20 years, which is of great concern because PMS programs that did not identify any findings were performed after an average of 3.5 years. A significant increase in mortality was due to diseases of the circulatory system (subarachnoid or intracerebral hemorrhage) or ill-defined conditions and to bone tumor-related mortality. The latter connection was found in three cases but has been confirmed in other studies after GH therapy (10, 19). However, safety of GH treatment with these background diagnosis in children have shown conflicting results, because Sävendahl et al (5) only recorded suicide and accidents in most deaths in a smaller, but similar study. A high GH dose, above 50 μg/kg · d, was consistently associated with increased mortality in the SAGhE study in analyses with both internal and external references. Children with extremely short stature, with a height SD score below −3 SD, also had a higher risk of mortality in univariate but not in multivariate analysis,

suggesting a possible role for intrinsic factors influencing mortality. It remains possible that an underlying disease associated with an increased risk of death may have been missed in some cases of very short stature. Overall, the authors mean that results do not allow the conclusion of a causal role of GH treatment in the findings (5), eg, it is possible that the findings reported do not have an identifiable biological basis and were random and/or pertain only to this French cohort (23).

As shown in Table 2, we are following different patient populations in the studies from Denmark and the United States (Refs 11 and 10, respectively). In the Danish study (11), the majority of the CO GHD population had a malignant background or a clear organic disease background (Table 2). In the US study (10), 40% had TS, CRI, and Other, and the rest ISS and IGHD. However, in both these studies CNS related tumors (recurrence or de novo), often in case of prior exposure or radiotherapy, was the main cause of death. This is in agreement with previous studies in children with previous malignancies (19). Thus, the severity of the underlying medical condition (OGHD and CRI) indicated the highest risk of death. Of importance is that among children, as in AO GHD with ACTH deficiency (8, 9), adrenal crises with mortal outcome were recorded.

Conclusions

After GH therapy, male AO GHD patients with a background of a nonfunctioning adenoma have no increased all-cause mortality, but women are still at a slightly higher risk. Increased mortality is seen in risk groups with a diagnosis of a craniopharyngioma, malignant causes of hypopituitarism, previous Cushing's disease, and patients with aggressive tumors. The main cause of increased mortality is cerebrovascular diseases. No risk increase of malignancies was recorded after GH therapy. There was a significant impact of young age at disease onset and of death from secondary brain tumors after conventional CRT.

In CO GHD cohorts, the long-term consequences of childhood GH therapy in patients with IGHD, ISS, and being born SGA are still a contradiction because one study recorded an increased mortality in circulatory disorders, ill-defined diseases and bone cancer, but in another study most deaths were due to suicide and accidents. In contrast, in CO GHD patients with an organic background, the mortality is increased. Thus, an underlying serious condition is the most important factor for death, with CNS tumors (recurrent or new tumor) as the leading cause of mortality. In addition, the fatal outcome of infectious dis-

eases in both CO and AO GHD patients with ACTH deficiency is still a clear threat.

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