LONG-TERM MORTALITY IN THE UNITED STATES COHORT OF PITUITARY-DERIVED GROWTH HORMONE RECIPIENTS

JAMES L. MILLS, MD, MS, LAWRENCE B. SCHONBERGER, MD, MPH, DIANE K. WYSOWSKI, PHD, PAUL BROWN, MD, STEPHEN J. DURAKO, BA, CHRISTOPHER COX, PHD, FANHUI KONG, PHD, AND JUDITH E. FRADKIN, MD

Objective **Patients who received pituitary-derived growth hormone (GH) are at excess risk of mortality from Creutzfeldt-Jakob disease. We investigated whether they were at increased risk of death from other conditions, particularly preventable conditions.**

Study design **A cohort (N = 6107) from known US pituitary-derived GH recipients (treated 1963–1985) was studied. Deaths were identified by reports from physicians and parents and the National Death Index. Rates were compared with the expected rates for the US population standardized for race, age, and sex.**

Results **There were 433 deaths versus 114 expected (relative risk [RR], 3.8; 95% confidence interval [CI], 3.4–4.2; $P < .0001$) from 1963 through 1996. Risk was increased in subjects with GH deficiency caused by any tumor (RR, 10.4; 95% CI, 9.1–12.0; $P < .0001$). Surprisingly, subjects with hypoglycemia treated within the first 6 months of life were at extremely high risk (RR, 18.3; 95% CI, 9.2–32.8; $P < .0001$), as were all subjects with adrenal insufficiency (RR, 7.1; 95% CI, 6.2–8.2; $P < .0001$). A quarter of all deaths were sudden and unexpected. Of the 26 cases of Creutzfeldt-Jakob disease, four cases have died since 2000.**

Conclusions **The death rate in pituitary-derived GH recipients was almost four times the expected rate. Replacing pituitary-derived GH with recombinant GH has eliminated only the risk of Creutzfeldt-Jakob disease. Hypoglycemia and adrenal insufficiency accounted for far more mortality than Creutzfeldt-Jakob disease. The large number of potentially preventable deaths in patients with adrenal insufficiency and hypoglycemia underscores the importance of early intervention when infection occurs in patients with adrenal insufficiency, and aggressive treatment of panhypopituitarism.** ***(J Pediatr 2004;144:430-6)***

In 1985, pituitary-derived growth hormone (pGH) was shown to transmit Creutzfeldt-Jakob disease (CJD), with fatal results.[1] In response to the CJD epidemic, we investigated mortality in the largest group of pGH recipients for whom long-term follow-up was available—all children treated with pGH provided through the National Hormone and Pituitary Program (NHPP) who could be traced—to assess the incidence of CJD and to identify other causes of mortality associated with growth hormone (GH), particularly preventable causes.

See editorial, p 415, and related article, p 437.

METHODS

The NHPP, a nationwide, centralized program for collection of human pituitary glands and extraction of GH, was the source of most GH used in the United States from 1963 until 1985. We undertook a systematic study in 1985 to identify persons treated with NHPP pGH and to investigate deaths in this cohort.[1,2] Treatment centers provided information on 6272 children confirmed to have received pGH. Medical information was obtained by standardized telephone interview or questionnaire for 84% of confirmed recipients in 1988. Deaths were identified through interview data, by contact with treating physicians and parents (to verify vital status and to ascertain the circumstances surrounding

CJD	Creutzfeldt-Jakob disease	NHPP	National Hormone and Pituitary Program
GH	Growth hormone	pGH	Pituitary-derived growth hormone
NDI	National Death Index	SMR	Standardized mortality ratio

From the National Institute of Child Health and Human Development, National Institute of Neurological Disorders and Stroke, and National Institute of Diabetes, Digestive and Kidney Diseases, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland; the US Food and Drug Administration and Westat, Rockville, Maryland; and the National Center for Infectious Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia.

The authors have no conflicts of interest.

Submitted for publication May 23, 2003; last revision received Oct 22, 2003; accepted Dec 24, 2003.

Reprint requests: James L. Mills, MD, MS, Chief, Pediatric Epidemiology Section, 6100 Building Room 7B03, NICHD, NIH, DHHS, Bethesda, MD 20892. E-mail: jamesmills@nih.gov.

0022–3476/$ - see front matter.

10.1016/j.jpeds.2003.12.036

deaths), and through a computerized linkage of the personal identifiers of NHPP pGH recipients with the National Center for Health Statistics National Death Index (NDI) to identify all deaths from January 1, 1979, through December 31, 1996. The NDI releases mortality data for a calendar year only after death information is processed for all the states, leading to a lag time between the end of the calendar year and release of data, but yielding virtually complete reporting of deaths when data are released.

Person-years of observation were calculated for each eligible recipient from the date of first pGH treatment to the date of last follow-up. Date at last follow-up was defined as (1) date of death if not later than December 31, 1996, (2) December 31, 1996 if the subject was known to be alive on January 1, 1979 (when NDI recording began) and no death was reported in the NDI, or (3) the last date seen by the treating physician if the recipient was not known to be alive on January 1, 1979. To avoid possible bias in death ascertainment, we truncated follow-up of all subjects on December 31, 1996.

Because CJD was a serious and unique factor associated with pGH, we continued to collect data from the ongoing search for CJD cases to the present. Cases occurring after December 31, 1996, are reported but are not included in the calculations of rates. Institutional review board approval was obtained for this study, as was informed consent from adult subjects or parents of minors.

Diagnostic Classification

The reason that each subject received pGH was ascertained from the treatment centers and in standardized interviews conducted with the GH recipients, their parents, or other family members in 1988.[1,2] We used this information to classify causes of GH deficiency as idiopathic, organic, or other. The organic group was subdivided into tumor or nontumor if another condition such as septo-optic dysplasia, histiocytosis, or trauma was present. Other categories were (1) GH-deficient, cause unknown; (2) other GH abnormality, such as bioinactive GH or neurosecretory defect; 3) no GH deficiency—for example, Turner syndrome; and (4) not classifiable.

Based on treatment center reports and interviews, subjects were classified as having (1) isolated growth hormone deficiency; (2) multiple pituitary hormone deficiency; (3) unspecified deficiency—that is, insufficient information to exclude multiple pituitary hormone deficiency; or (4) not applicable, for GH recipients without growth hormone deficiency. Treatment centers identified subjects with hypoglycemia. Adrenal insufficiency was identified via interview data on glucocorticoid replacement therapy.

Analytical Methods

Observed mortality was compared with the overall mortality and the cancer mortality (http://seer.cancer.gov/1973_1999/) that would have been expected in a US general population cohort of similar composition.[3] Specifically, mortality rates were standardized by sex, race (black or nonblack), age, and calendar year of observation. Person-years of observation were calculated for each subject from the date of first pGH therapy to the date of last follow-up as defined. Each person-year was categorized by sex, race, age, and calendar year. For subjects whose race was unknown, nonblack race was imputed, because more than 90% of subjects with known race were nonblack. Repeating the analysis without those with imputed race did not substantially alter the findings. The standardized mortality ratio (SMR) relative risk (RR) was calculated by dividing the observed mortality by the expected mortality. For observed counts of $\leq$20, 95% CIs for the SMR were computed by using exact methods for the Poisson distribution. For observed counts >20, an asymptotic method based on the log transformation was used.

Relative risks of mortality were calculated for subgroups based on cause of GH deficiency (eg, idiopathic, organic/tumor), type of hormonal deficiency (isolated or multiple), diagnosis of hypoglycemia (yes or no), diagnosis of adrenal insufficiency (yes or no), and age group (for populations at particular risk such as infants with hypoglycemia). A proportional hazards model was used to confirm the contribution of these risk factors. Time 0 for each recipient was the date of first pGH treatment. In addition to these risk factors, the demographic factors of interest were also included in the model. Because of collinearity, we also examined data on individual cases of particular interest, such as sudden, unexpected deaths, to develop clinical profiles. These profiles were used to identify the most clinically important factors from among those in the SMR and proportional hazards analyses.

Kaplan-Meier survival curves, implemented in SAS 6.11 (SAS Institute, Cary, NC) were plotted to demonstrate the mortality pattern in important subgroups.

Causes of Death

Death certificates were obtained for all but three deaths in the cohort. Medical records were obtained for 76% and reviewed by a study physician (J. F.). Physicians or family members were called to obtain more detailed information when the cause of death was not clear or when CJD was the presumed diagnosis. Physicians with expertise in diagnosing CJD reviewed all medical records that documented neurologic signs or symptoms in the year before death. Two neuropathologists independently reviewed all available neuropathology specimens. Deaths were grouped for analysis by cause based on International Classification of Diseases-9 codes and physician review.

One hundred sixty-five recipients were excluded from statistical analysis because they did not have sex, year of birth, year of first GH treatment, or year of last follow-up available, yielding 6107 subjects eligible for standardized mortality analysis.

RESULTS

The characteristics of the cohort and underlying conditions causing organic GH deficiency are listed in Table I.

Table I. Characteristics of NHPP Cohort

	N	%	Age at treatment (y)
Total cohort identified	6272		
Included in mortality analysis	6107	100	10.2 ± 4.7
Sex			
Male	4192	69	10.4 ± 4.7
Female	1915	31	9.6 ± 4.6
Race			
Black	434	7	9.9 ± 5.3
Non-black	5421	89	10.2 ± 4.6
Imputed as non-black	252	4	10.6 ± 4.6
Cause of GHD			
Idiopathic	3387	55	9.8 ± 4.8
Organic with tumor	1078	18	11.8 ± 3.9
Organic without tumor	612	10	9.3 ± 5.2
GHD unspecified cause	159	3	9.4 ± 4.8
Possible GH abnormality	97	2	9.7 ± 4.0
Not GHD	434	7	10.3 ± 3.8
Not classifiable/Missing	340	6	10.5 ± 4.1
Type of GHD			
Isolated	1798	30	10.2 ± 4.2
Multiple	3320	54	10.1 ± 5.0
Not specified	118	2	10.0 ± 4.7
Not applicable	871	14	10.3 ± 4.0
Hypoglycemia			
Yes	296	5	4.1 ± 3.8
No	5811	95	10.5 ± 4.5
Adrenal insufficiency			
Yes	1419	23	10.0 ± 5.4
No	4688	77	10.2 ± 4.4
Reason for organic GHD*	1690	100	
Organic with tumor (64%)			
Leukemia	43	3	
Craniopharyngioma	348	21	
Lymphoma or Hodgkin's disease	16	1	
Other malignant tumor	288	17	
Unknown, tumor-related specified by physician	397	24	
Organic without tumor (36%)			
Septo-optic dysplasia	88	5	
Histiocytosis/Hand-Schuller-Christian Disease	27	2	
Head injury causing growth problem	95	6	
Unknown, organic specified by physician	407	24	

GHD, Growth hormone deficiency.
*Some recipients have more than one reason.

There were 433 deaths from all causes from 1963, when treatment began, through December 31, 1996, in the 6107 subjects, who provided 105,797 person-years of follow-up. The expected number of deaths based on general population mortality rates was 114, giving the pGH subjects an overall risk of death almost four times higher than the general population comparison group (RR, 3.8; 95% CI, 3.4-4.2; $P < .0001$).

Only subjects with idiopathic, isolated GHD had an observed death rate that was not significantly different from the expected (RR, 1.3; 95% CI, 0.9-1.7). All other major subgroups of recipients had significantly elevated death rates compared with the general population (Table II).

The highest risk groups were those with benign or malignant tumors, adrenal insufficiency, and hypoglycemia. Patients who had hypoglycemia and received pGH before 6 months of age were at extremely high risk (Figure; RR, 18.3; 95% CI, 9.2-32.8; $P < .0001$).

Proportional hazards analysis also demonstrated that tumors, hypoglycemia, adrenal insufficiency, and multiple hormone deficiencies were significant, independent risk

Table II. Relative risk of mortality by subgroup of cohort†

	N	Observed/Expected mortality	Relative risk	
			95% CI	*P* value*
Total cohort	6107	433/114	3.8 (3.4, 4.2)	< .0001
All idiopathic	3387	130/67.4	1.9 (1.6, 2.3)	< .0001
Idiopathic-isolated	1648	38/30.2	1.3 (0.9, 1.7)	.08
Idiopathic-multiple	1735	92/37.1	2.5 (2.0, 3.0)	< .0001
Organic/Tumor	1078	200/19.2	10.4 (9.1, 12.0)	< .0001
Organic/Tumor-isolated	57	13/0.9	14.4 (7.7, 24.7)	< .0001
Organic/Tumor-multiple	1005	185/18.1	10.2 (8.8, 11.8)	< .0001
Organic/No Tumor	612	52/9.4	5.5 (4.2, 7.3)	< .0001
Organic/No tumor-isolated	84	4/1.3	3.1 (0.8, 7.9)	NS
Organic/No tumor-multiple	506	44/7.9	5.6 (4.1, 7.5)	< .0001
Hypoglycemia	296	32/3.3	9.7 (6.9, 13.7)	< .0001
Adrenal insufficiency	1419	194/27.3	7.1 (6.2, 8.2)	< .0001

*One-tailed test.
†pGH type information was missing for four idiopathic, 16 organic tumor, and 22 organic nontumor subjects.

factors (data not shown). Many subjects, however, had multiple risk factors such as tumors causing hypopituitarism with adrenal insufficiency that resulted in collinearity.

To identify preventable causes of death and to determine how they might be avoided in the future, we looked for critical risk factors. We examined death certificates, autopsy reports, medical records, and interview data from treating physicians and families for each subject who had a sudden, unexpected death. This information was used to identify medical problems that put subjects at high risk and to determine what medical findings or symptoms immediately preceding death could be useful to alert clinicians to the danger.

A surprisingly high number of all deaths, 106 (24.5%), were sudden and unexpected. The presence of multiple hormone deficiencies was specifically mentioned in 74% of these deaths, hypoglycemia in 31%, and seizures in 52%. Notably, 59 of the 106 (56%) deaths had a clinical course strongly suggestive of adrenal insufficiency. There were 32 (30%) deaths associated with infections ranging from clearly life-threatening (epiglottitis, sepsis) to generally benign (upper respiratory infection, gastroenteritis); adrenal insufficiency was the likely cause of death in 29 of the 32. All 16 cases in which vomiting was reported during the final illness had features indicating that adrenal insufficiency was the cause of death. There were 35 cases (33%) in which the subject was discovered dead or comatose; 30 were suspicious of adrenal insufficiency. In 12 patients, there were definite indications of an inadequate therapeutic response to impending adrenal crisis: failure to take steroids, failure to increase the dose of steroids, or failure to get parenteral steroids during episodes of vomiting or other illness.

The second important risk factor in our cases of sudden, unexpected death was the presence of another medical condition. In all, 58% of patients who died suddenly had a problem beyond simple GH deficiency that was not considered life-threatening: 25 (24%) had craniopharyngiomas, and 15 (14%) had other intracranial tumors. Seizure disorders were present in 20 sudden deaths in subjects who did not have adrenal insufficiency.

The death rate in children younger than 6 years who had hypoglycemia remained stable between one death per 31 person-years and one death per 54 person-years over the 15-year period (1975–1989) when there were a sufficient number of subjects in this age group to determine rates. Contrary to our expectations, the death rate in subjects with adrenal insufficiency did not drop as the children got older; the death rate was stable between 1975 and 1996, between one death per 173 person-years and one death per 113 person-years.

Other than these unexpected deaths, the substantial increase in mortality in those with organic causes of GH deficiency was a result of recurrence or complications of their neoplasms, congenital disorders, or other problems that caused GH deficiency. There were 21 deaths from second neoplasms with onset after GH therapy in patients who had a pre-existing malignancy or craniopharyngioma as the cause of GH deficiency. The data are shown in Table III. Given a recent report that pGH recipients in the United Kingdom were at significantly increased risk of death from colorectal cancer,[4] it is noteworthy that two subjects in our cohort died of colorectal cancer. The first was clearly unrelated to GH; the patient had familial polyposis. The second patient had received radiation for a brain tumor. If both patients are excluded as having risks that made GH an unlikely cause or contributor to their cancer deaths, there is obviously no increased risk for colorectal cancer death in our cohort. If the second patient is not excluded, the observed number of events is one, and the expected rate is 0.35 deaths (odds ratio [OR], 5.7; CI, 0.69-20.64, *P* = NS). Thus, we did not find a significant excess risk

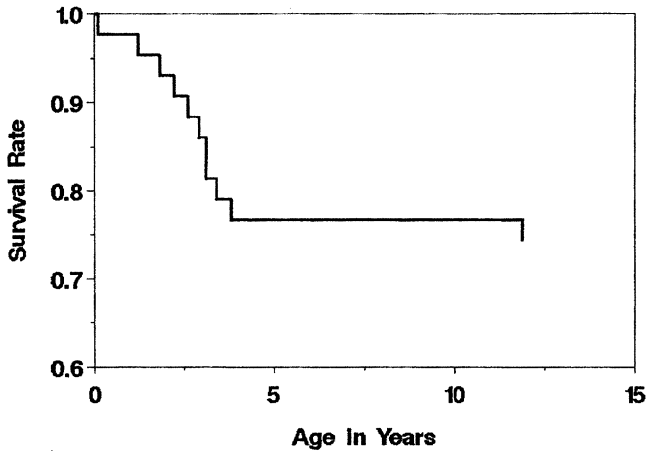

Figure. Survival rates for subjects with hypoglycemia who began treatment between birth and 6 months of life.

of death from colorectal cancer related to GH. An excess of death as a result of Hodgkin's disease has also been reported.[4] Our cohort had one death (expected, 0.40) for an OR of 2.5 (CI, 0.06-13.93; P = NS). There were five deaths from osteogenic sarcoma in our cohort; however, four were second tumors in subjects who had received large doses of radiation and chemotherapy.

We examined the risk of cancer deaths in GH recipients who did not have previous tumors. Nine cancer deaths occurred in this group versus 8.33 expected (OR, 1.1; CI, 0.49-2.05). After excluding those with other risk factors—undescended testes-testicular cancer, smoking-lung cancer, and Noonans syndrome-Burkitt's lymphoma—there were six fatal cases (OR, 0.7; CI, 0.26-1.57).

We identified 26 subjects who died of CJD among NHPP GH recipients. There are 12 cases in our cohort who died before 1997 and nine who died subsequently. Our surveillance also identified five patients with CJD for whom NHPP records show GH was awarded but who could not be identified or confirmed as treated by treatment centers at the start of the study and are not in the cohort being followed and analyzed. No cases have occurred in subjects who began treatment after 1977, when the method of GH production was changed to include size exclusion chromatography purification.

DISCUSSION

Creutzfeldt-Jakob disease is the best known but far from the most common cause of death in pGH recipients. The death rate in the US pGH cohort was almost four times the expected rate, and many more deaths occurred from hypoglycemia, adrenal insufficiency, and other potentially preventable causes than from CJD. Indeed, one quarter of all deaths were unexpected and sudden. In newly treated patients, the use of recombinant DNA GH has eliminated the risk of CJD, but not the risk for these other causes of death. Perhaps surprisingly, the risk of death from adrenal insufficiency remained stable throughout the period of observation despite the maturation of the cohort.

Table III. Deaths from malignancies with onset after GH therapy

Etiology of growth failure*	Neoplasm
Subjects with previous tumor/malignancy	
Unspecified brain tumor/RT	Colon
Angiofibroma nasopharynx/RT	Colon
Neurofibromatosis	Fibrosarcoma
Brain tumor/RT	Rhabdomyosarcoma
Diffuse histiocytic lymphoma/RT/CHEMO	Osteogenic sarcoma
Pineal germinoma/RT/CHEMO	Osteogenic sarcoma
Retinoblastoma/RT/CHEMO	Osteogenic sarcoma
Medulloblastoma/RT/CHEMO	Osteogenic sarcoma
Craniopharyngioma/RT	Glioma
Craniopharyngioma	Squamous cell
Craniopharyngioma/RT	Lymphoma
Craniopharyngioma/RT	Leukemia
Craniopharyngioma/RT	Leukemia
Astrocytoma/RT/CHEMO	Leukemia
Neurofibromatosis	Leukemia
Leukemia	Astrocytoma
Craniopharyngioma/RT	Oligodendroglioma
Craniopharyngioma/RT	Astrocytoma/Glioma
Craniopharyngioma	Glioma
Leukemia	Glioma
Rhabdomyosarcoma	Adrenal
Subjects without previous tumor	
Idiopathic	Nasopharyngeal
Septo-optic dysplasia	Nasopharyngeal
Idiopathic intrauterine growth restriction	Osteogenic sarcoma
Male Turner's (Noonan's syndrome)	Burkitt's lymphoma
Idiopathic	T-cell lymphoma
Idiopathic	Lung cancer (smoker)
Idiopathic/Undescended testes	Germ cell
Idiopathic	Hodgkin's lymphoma
Idiopathic	Leukemia

CHEMO, Chemotherapy; *RT*, radiation of previous tumor.
*Risk factors are noted when they were available from medical records.

The large size of this cohort and the long duration of follow-up made it possible for the first time to quantify the increased risk of death from adrenal crisis, hypoglycemia, and other complications of hypopituitarism, and to analyze the time course of this mortality systematically. We were also able to examine unexpected deaths in detail to identify specific factors to alert clinicians and patients to high-risk situations.

Hypoglycemia was an important marker of high risk for death. Children with hypoglycemia had a ninefold increase in risk, mainly in the first years of life and of treatment. Many of these deaths resulted from a combination of hypoglycemia, seizures, aspiration, and possible adrenal insufficiency in children with panhypopituitarism. The risk decreased as children reached the age at which they could identify and respond to symptoms of hypoglycemia. Thus, physicians should alert parents to the very high risk of death during infancy and monitor and treat aggressively.

Tumors were a second important cause of death. Some subjects had been given pGH on the assumption that they had been cured, but they died of recurrence or second malignancies. Even patients whose tumors were not considered dangerous were at risk for sudden and unexpected death. On the other hand, our cohort did not have a significantly increased death rate that could be related to GH from either colorectal cancer or Hodgkin's disease, the two cancers that occurred significantly more often than expected in the United Kingdom cohort of GH recipients.[4] Bearing in mind the small number of colorectal cancer and Hodgkin's disease deaths, we find no evidence that GH therapy increases the risk of death from these conditions, or the risk of death from all cancers in those without predisposing risk factors.

The third, and perhaps most striking, risk factor was adrenal insufficiency. More than half of the sudden, unexpected deaths appeared to be adrenal insufficiency-related. Adrenal insufficiency, unlike hypoglycemia, continued to cause deaths into adulthood. Thus, those caring for adolescents and adults in addition to younger children should note the clinical features we identified that were warning signs of life-threatening adrenal insufficiency. Physicians and families must be made aware that failure to treat illnesses with adrenal steroid replacement in adequate doses can be fatal. Moreover, increased doses of oral therapy or parenteral therapy may be necessary for even "trivial" infections. Deaths occurred in our cohort after URIs, gastroenteritis, and pneumonia. Vomiting was a dangerous symptom, possibly because it interfered with the delivery of oral steroids. Seizures also contributed to a number of sudden deaths. Our data underscore the need to initiate therapy promptly; of the 35 subjects found dead or comatose by families or friends, 30 (86%) probably died from unrecognized or inadequately treated adrenal insufficiency.

Adrenal crisis requires prompt, vigorous treatment. Correction of hypovolemia, hypoglycemia, and hyponatremia is accomplished by infusing 5% dextrose/0.9% sodium chloride, as a bolus dose of 20 mL/kg followed by at least twice maintenance.[5] Prompt treatment with intravenous hydrocortisone 25 to 50 mg/sq. M is critical for correcting the underlying glucocorticoid deficit, and additional glucose may be needed for hypoglycemia. After the patient recovers, expert management is required to insure adequate glucocorticoid replacement without suppressing growth. Arlt and Allolio[6] report that their adult patients had 3.3 adrenal crises severe enough to require hospitalization per 100 patient-years. Thus, patient education and compliance are critical issues. The same authors recommend regular crisis prevention training that emphasizes the need to wear bracelets, increase hydrocortisone for stressful activities including minor illnesses, and get parenteral therapy for gastroenteritis, trauma, or serious illnesses. Our experience demonstrates the need for rapid initiation of parenteral hydrocortisone, a point that must be made repeatedly to patients and parents because of the compliance problem. Because parenteral therapy may be lifesaving, some groups recommend that adult patients be given hydrocortisone for emergency self-injection, a recommendation that could be applied equally to families of children at risk.

Other studies of GH recipient populations in Canada,[7] the United Kingdom,[8] and France[9] also found deaths caused by hypopituitarism. In those reports, which studied fewer subjects for shorter durations, hypopituitarism accounted for 24% (9/37), 12% (13/110), and 6% (2/31) of all deaths, respectively. Clearly, greater awareness of the risk of death from these complications on the part of patients and health care providers would benefit all patients with hypopituitarism, not just this population.[10]

There is considerable interest in the long-term outcomes of pGH recipients because of transmission of CJD through pituitary preparations[11,12] and the increasing use of GH as a result of the availability of virtually unlimited supplies of biosynthetic hormone.[13] The tragic occurrence of CJD is a major concern in the NHPP GH recipient population. Unfortunately, nothing currently can mitigate this risk. Four new CJD cases have died since 2000; however, we still do not know how many NHPP pGH recipients will eventually contract CJD. Approximately half of the potentially exposed patients have not yet attained the median incubation period of 21.5 years observed thus far in the study; for some cases, the incubation period can be 30 years after exposure to GH.[14] Over the time course of this study, however, CJD accounted for only 3% of the mortality in this population. In contrast, there has been a much greater mortality from preventable manifestations of hypopituitarism.

In summary, this study showed that pGH recipients are at greatly increased risk of dying, not only because of the tumors and other conditions that made them GH-deficient, but also because of sudden, unexpected deaths caused in large part by hypoglycemia and adrenal insufficiency. Our data show that physicians treating patients with adrenal insufficiency and the patients themselves must react quickly to even mild infections, particularly those associated with vomiting. Without adequate glucocorticoid replacement, delivered parenterally if necessary, such infections can be fatal. Similarly, hypoglycemia and panhypopituitarism in infants and young children must be managed aggressively. Skilled management of these two problems can substantially decrease death rates in patients with hypopituitarism.

We thank the patients, their physicians, and their families for making this study possible. David Chang and Margaret Camarca from Westat provided valuable technical assistance.

REFERENCES

1. Mills JL, Fradkin J, Schonberger L, Gunn W, Thomson RA, Piper J, et al. Status report on the U.S. human growth hormone recipient follow-up study. Horm Res 1990;33:116-20.

2. Fradkin JE, Schonberger LB, Mills JL, Piper JM, Wysowski DK, Thomson R, et al. Creutzfeldt-Jakob disease in pituitary growth hormone recipients in the United States. JAMA 1991;265:880-4.

3. National Center for Health Statistics. Vital Statistics of the United States. Vol. II. Mortality. Part B. Washington, DC: Public Health Service; 1996.

4. Swerdlow AJ, Higgins CD, Adlard P, Preece MA. Risk of cancer in patients treated with human pituitary growth hormone in the UK, 1959-85: a cohort study. Lancet 2002;360:273-7.

5. Kappy MS, Bajaj L. Recognition and treatment of endocrine/metabolic emergencies in children: part I. Adv Pediatr 2002;49:245-72.
6. Arlt W, Allolio B. Adrenal insufficiency. Lancet 2003;361:1881-93.
7. Taback SP, Dean HJ, Canadian Growth Hormone Advisory Committee. Mortality in Canadian children with growth hormone (GH) deficiency receiving GH therapy 1967-1992. J Clin Endocrinol Metab 1996;81:1693-6.
8. Buchanan CR, Preece MA, Milner RD. Mortality, neoplasia and Creutzfeldt-Jakob disease in patients treated with human pituitary growth hormone in the United Kingdom. BMJ 1991;302:824-8.
9. Goujard J, Entat M, Maillard F, Mugnier F, Rappaport R, Job JC. Human pituitary growth hormone (hGH) and Creutzfeldt-Jakob disease: results of an epidemiological survey in France, 1986. Int J Epidemiol 1988;17:423-7.
10. Hintz RL. Eternal vigilance-mortality in children with growth hormone deficiency. J Clin Endocrinol Metab 1996;81:1691-2.
11. Brown P, Gajdusek DC, Gibbs CJ Jr, Asher DM. Potential epidemic of Creutzfeldt-Jakob disease from human growth hormone therapy. N Engl J Med 1985;313:728-31.
12. Gibbs CJ Jr. Creutzfeldt-Jakob disease and related transmissible spongiform encephalopathies. N Engl J Med 1998;339:1994-2004.
13. Vance ML, Mauras N. Growth hormone therapy in adults and children. N Engl J Med 1999;341:1206-16.
14. Brown P, Preece M, Brandel J-P, Sato T, McShane L, Zerr I, et al. Iatrogenic Creutzfeldt-Jakob disease at the millennium. Neurology 2000;55:1075-81.

50 Years Ago in *The Journal of Pediatrics*

PAINLESS INJECTIONS IN PEDIATRIC PRACTICE

MacKenzie EP. J Pediatr 1954;44:421

Although much recent attention has been given to the recognition and management of pain in children and infants, Dr Ellen MacKenzie proposed a method of alleviating the pain of injections in 1954! At the time, pediatricians often accepted theories that infants and toddlers are incapable of feeling pain. Dr MacKenzie recognized the pain that her pediatric patients experienced during injections and provided localized analgesia by freezing a 1:1000 solution of Zephiran in ice cubes. Zephiran, benzalkonium chloride, is a cationic detergent used primarily as a topical disinfectant and as a preservative. The frozen solution was then rubbed on the patients' skin before injections for localized analgesia. She acknowledged that this approach could only provide temporary pain relief.

Today pediatricians are faced with the same dilemma of providing medical care without inflicting pain. Topical anesthetics have been developed and are effective in reducing or eliminating pain associated with injections, such as a commonly used topical anesthetic eutectic mixture of local anesthetics (EMLA), consisting of lidocaine and prilocaine in a cream preparation. EMLA cream must be applied 1 hour before procedures and 2 hours before intramuscular injections to have an analgesic effect. Vapocoolant sprays, similar to the technique utilized by Dr MacKenzie, also are used effectively. Another current analgesic approach is lidocaine iontophoresis, which allows for the active transdermal delivery of lidocaine under the influence of a low-level electric current. Unfortunately, anxiety associated with injections continues to be a problem. Patient anxiety may be reduced with the use of topical anesthetics, whenever medically possible, with all injections.

Dr MacKenzie acknowledged that her technique had no effect on subsequent pain and stiffness or the pain of injection of large volumes of solutions. Even today, pediatricians do not have an analgesic that effectively eliminates pain associated with intramuscular injections, especially when large volumes of medications are delivered. Topical analgesics have made injections for pediatric patients less traumatic and decreased the overall anxiety associated with future injections. Dr MacKenzie was a pioneer in the recognition of pain management within her practice, during a time when little focus was placed on pediatric pain.

Janey P. McGee, MD
F. Bruder Stapleton, MD
Department of Pediatrics
University of Washington
Seattle, WA 98105
YMPD723
10.1016/j.jpeds.2004.01.014