

CLINICAL STUDY

Direct causes of death in Japanese patients with hypopituitarism as analyzed from a nation-wide autopsy database

Hidesuke Kaji and Kazuo Chihara¹

Division of Physiology/Metabolism, College of Nursing Art and Science, Hyogo, Akashi, Japan and ¹Division of Endocrinology/Metabolism, Neurology and Hematology/Oncology, Kobe University Graduate School of Medicine, Kobe, Japan

(Correspondence should be addressed to H Kaji, Division of Physiology/Metabolism, College of Nursing Art and Science, Hyogo 13-71, Kitaohji-cho, Akashi 673-8588, Japan; Email: hidesuke_kaji@cnas-hyogo.ac.jp)

Abstract

Objectives: The direct causes of death in Japanese patients with hypopituitarism remain unclear. In this study, the direct causes of death were investigated and compared between Japanese patients with hypopituitarism from a nation-wide autopsy database and an age- and gender-matched control population from national reports.

Subjects: Three hundred and ninety-one subjects with hypopituitarism who had died were selected from a nation-wide autopsy database (1984–1993). The ratios of each cause of death among the age- and gender-matched control population were derived from national reports.

Results: In subjects with hypopituitarism, an increased relative frequency of death from cerebrovascular diseases (male; 2.02 (95% confidence interval (CI) 1.45–2.82), female; 1.73 (95% CI 1.18–2.52)) was found. In particular, the relative frequency of death from cerebral hemorrhage was 4.60 (95% CI 2.95–7.17) in male and 4.80 (95% CI 2.90–7.94) in female subjects with hypopituitarism. Unexpectedly, a decreased relative frequency of death from all heart diseases (male; 0.439 (95% CI 0.277–0.696), female; 0.267 (95% CI 0.149–0.478)) was found in subjects with hypopituitarism, although there was no difference between subjects with hypopituitarism and controls in the frequency of death from ischemic heart disease.

Conclusions: These results provide useful information for the long-term care of Japanese patients with hypopituitarism.

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Introduction

Four retrospective (1–4) and one prospective (5) epidemiological studies have examined mortality among patients with hypopituitarism and all have reported premature mortality mainly from cardiovascular or cerebrovascular disease. In particular, Tomlinson *et al.* (5) identified several factors (age at diagnosis, gender, a diagnosis of craniopharyngioma and untreated gonadotropin deficiency) affecting increased mortality.

On the other hand, adult growth hormone (GH) deficiency (AGHD) is a syndrome (6) characterized by increased visceral adipose tissue, decreased muscle mass as well as bone mineral density, hyperlipidemia and increased intima and media thickness of the carotid artery (7, 8). Many of these are risk factors for cardiovascular disease or stroke. Although the replacement with GH for AGHD is known to have

beneficial effects on atherosclerosis (6) or cardiac functions (9–12), there is no evidence supporting the effect of GH replacement on mortality. Therefore, the replacement of GH or not, for GH-deficient adults (13, 14), is still under discussion. The prognosis of AGHD still remains to be clarified in Japan, where the environmental and genetic background is somewhat different from Europe and America. Although we carried out a longitudinal follow-up or cross-sectional investigation by questionnaire among AGHD subjects in Japanese hospitals of endocrinology and metabolism, the number of deaths among patients with AGHD was insufficient to analyze statistically (15). In the present study, we examined the direct causes of death in patients with hypopituitarism from the autopsy database of the past decade in Japan and compared those results with age- and gender-matched controls from annual reports of the Health and Welfare Statistics Association (16, 17).

Subjects and methods

The autopsy database of the past decade (1984–1993) contained 812 subjects in whom hypopituitarism was included as a pathological diagnosis. Cushing's disease, acromegaly or direct invasion of pituitary tumors were considered to be a direct cause of death in 421 of the 812 subjects. Three hundred and ninety-one subjects with hypopituitarism were therefore enrolled in the present study after subtraction of the other 421 subjects. The median age at death (range) was 61 (1–89) years in 221 males and 54 (1–89) years in 170 females. The distribution of various causes of death in age- and gender-matched control populations was derived from the national reports of the Health and Welfare Statistics Association in 1986 (16) and 1991 (17), where the number of deaths per 100 000 people from each cause was corrected according to the age and gender distribution of subjects with hypopituitarism.

The direct causes of death were compared between subjects with hypopituitarism and the age- and gender-matched controls by estimating an odds ratio with a 95% confidence interval (CI). Statistical analysis was performed using the SPSS for Windows software package (Nankodo, Tokyo).

Results

Table 1 shows the numbers of deaths from each cause of death in subjects with hypopituitarism and odds ratios with 95% CI, compared with those in the age- and gender-matched controls. Vascular disease is considered of potential importance as the cause of death in patients with hypopituitarism. The relative frequency of death from total circulatory disease in male subjects with hypopituitarism was not statistically different from that in controls (0.986 (95% CI 0.735–1.32)), but was rather lower in female subjects

Table 1 Direct causes of death from an autopsy database in subjects with hypopituitarism.

Causes of death	Male (n = 221)		Female (n = 170)	
	No. of deaths	Odds ratio (95% CI)	No. of deaths	Odds ratio (95% CI)
Circulatory	73	0.986 (0.735–1.32)	57	0.700 (0.149–0.985)*
Hypertension	0	—	0	—
Heart	21	0.439 (0.277–0.696)*	13	0.267 (0.149–0.478)*
Ischemic heart disease	8	0.533 (0.258–1.10)	6	0.502 (0.214–1.17)
Others	13	—	7	—
Cerebrovascular	52	2.02 (1.45–2.82)*	44	1.73 (1.18–2.52)*
Hemorrhage	31	4.60 (2.95–7.17)*	29	4.80 (2.90–7.94)*
Infarct	21	1.45 (0.896–2.34)	15	0.907 (0.513–1.60)
Others	0	—	0	—
Neoplasm	63	0.901 (0.664–1.22)	42	0.874 (0.603–1.27)
Lung	18	1.19 (0.714–1.98)	4	0.752 (0.263–2.15)
Gastrointestinal	13	0.591 (0.332–1.05)	8	0.705 (0.332–1.49)
Liver and pancreas	3	0.232 (0.073–0.736)*	4	0.590 (0.208–1.67)
Breast	0	—	3	1.07 (0.312–3.71)
Uterus	—	—	2	0.900 (0.202–4.01)
Leukemia	4	3.42 (1.09–10.7)*	0	—
Others	25	—	21	—
Respiratory	38	1.48 (1.02–2.14)*	27	0.818 (0.527–1.27)
Pneumonia	31	1.45 (0.969–2.17)	21	0.673 (0.415–1.09)
Chronic obstructive pulmonary disease	1	0.176 (0.024–1.28)	0	—
Others	6	—	6	—
Digestive	8	1.14 (0.54–2.39)	12	2.47 (1.24–4.92)*
Peptic ulcer	4	4.07 (1.27–13.1)*	3	4.02 (0.930–17.4)
Liver	3	0.578 (0.179–1.87)	6	1.84 (0.727–4.64)
Others	1	—	3	—
Renal	2	0.440 (0.106–1.83)	3	0.725 (0.216–2.43)
Metabolic	8	3.33 (1.48–7.49)*	6	2.27 (0.88–5.87)
Diabetes mellitus	5	2.17 (0.818–5.76)	2	0.767 (0.175–3.37)
Others	3	—	4	—
External cause	3	0.266 (0.084–0.845)*	2	0.253 (0.061–1.05)
Accident	3	0.414 (0.129–1.33)	2	0.473 (0.111–2.01)
Suicide	0	—	0	—
Others	0	—	0	—
Other causes	26	—	21	—

* Relative frequency of death by each cause is significantly different from age- and gender-matched controls derived from national demographic reports.

than in the corresponding controls (0.700 (95% CI 0.149–0.985)). In the case of circulatory disease, the relative frequency of death from total heart diseases was rather lower in subjects with hypopituitarism than among controls (male; 0.439 (95% CI 0.277–0.696), female; 0.267 (95% CI 0.149–0.478)), although the ratio of death from ischemic heart disease was not statistically different between subjects and controls (male; 0.533 (95% CI 0.258–1.10), female; 0.502 (95% CI 0.214–1.17)). In contrast, the relative frequency of death from cerebrovascular disease was higher in subjects with hypopituitarism than among controls (male; 2.02 (95% CI 1.45–2.82), female; 1.73 (95% CI 1.18–2.52)). In cerebrovascular disease, the relative frequency of death from cerebral hemorrhage was higher in patients with hypopituitarism than among controls (male; 4.60 (95% CI 2.95–7.17), female; 4.80 (95% CI 2.90–7.94)). Unexpectedly, the ratio of death from cerebral infarction was not different between patients and controls (male; 1.45 (95% CI 0.896–2.34), female; 0.907 (95% CI 0.513–1.60)).

The relative frequency of death from neoplasm in subjects with hypopituitarism was not statistically different from that in controls (male; 0.901 (95% CI 0.664–1.22), female; 0.874 (95% CI 0.603–1.27)). The relative frequency of death from neoplasm of the liver and pancreas was lower in male subjects with hypopituitarism than among controls (0.232 (95% CI 0.073–0.736)). In contrast, the relative frequency of death from leukemia was slightly but significantly higher in male subjects with hypopituitarism than among controls (3.42 (95% CI 1.09–10.7)). The relative frequency of death from total respiratory diseases was higher in male subjects with hypopituitarism (1.48 (95% CI 1.02–2.14)). The relative frequency of death from digestive diseases was higher in female subjects with hypopituitarism than among controls (2.47 (95% CI 1.24–4.92)). In digestive diseases, the relative frequency of death from peptic ulcer was higher in male subjects with hypopituitarism than in controls (4.07 (95% CI 1.27–13.1)). Although the relative frequency of death from diabetes mellitus in subjects with hypopituitarism was not statistically different from that in controls, the relative frequency of death from total metabolic diseases was higher, especially in male subjects with hypopituitarism, than in controls (3.33 (95% CI 1.48–7.49)). The relative frequency of death from external causes was lower in male subjects with hypopituitarism than in controls (0.266 (95% CI 0.084–0.845)), although the relative frequency of death caused by accidents in subjects with hypopituitarism was not statistically different from that in controls (0.414 (95% CI 0.129–1.33)). The relative frequency of death from renal disease in subjects with hypopituitarism was not statistically different from controls (male; 0.440 (95% CI 0.106–1.83), female; 0.725 (95% CI 0.216–2.43)).

Discussion

This is the first epidemiological study to correlate demographic data with autopsy reports on hypopituitarism. In this study, the relative frequency of death from cerebrovascular disease was higher in subjects with hypopituitarism than in controls, in good agreement with previous reports (3, 5). Among deaths from cerebrovascular disease, cerebral hemorrhage was notably higher in subjects with hypopituitarism than in controls. Patients whose death might be caused by hypothalamic–pituitary tumor invasion were not enrolled in the study. However, we cannot exclude the possibility that the tumor invasion or their treatment modality directly or indirectly influenced the pathogenesis of cerebral hemorrhage. Several investigators have reported an association between pituitary radiotherapy and stroke (18–20). It is surprising that the ratio of death not only by cerebral infarction but also by ischemic heart disease was no different in patients and controls, since the pathogenesis of these diseases is based on atherosclerosis, which is considered to be more extensive in hypopituitarism (6). We have also recently reported (8) that GH deficiency appears to increase an atherosclerotic risk in Japanese AGHD subjects as with Caucasians and to cause more extensive carotid intima-media thickening in child-onset AGHD than in adult-onset AGHD.

The relative frequency of death from total neoplasm in subjects with hypopituitarism was not statistically different from that in controls, consistent with previous reports (5). It remains unclear why the relative frequency of death from neoplasm of the liver and pancreas was lower in male patients with hypopituitarism. One of the deficient but not replaced hormone may be GH in subjects with hypopituitarism. If GH plays a role in the stimulation of cell growth in digestive organs, GH deficiency might cause a suppression of cell growth, resulting in a lower ratio of death from neoplasm of the liver and pancreas. However, this explanation is not relevant for females or for other types of neoplasm, and is contrary to the higher prevalence of death by leukemia in male patients with hypopituitarism. It is suspected, but remains unclear, as to whether GH replacement in GH-deficient children causes a greater susceptibility to leukemia.

The relative frequency of death from peptic ulcer was higher in male subjects with hypopituitarism than in controls. This is the first report of this finding to our knowledge and suggests that patients with hypopituitarism are more susceptible to stress, although hypercortisolemia may not appear in most patients with hypopituitarism but only in patients with hypopituitarism who have intact pituitary–adrenal axes.

The relative frequency of death from total respiratory diseases was higher in male subjects with hypopituitarism than in controls. Tomlinson *et al.* (5) have reported an increase in respiratory mortality in subjects with

hypopituitarism. Judging from their report, it is unlikely that the inadequate corticosteroid hormone replacement played an important role in this factor, since respiratory mortality did not differ significantly between patients who had intact versus those who had deficient pituitary–adrenal axes. The relative frequency of death from pneumonia did not differ between subjects with hypopituitarism and controls, suggesting that a decrease in immune functions in hypopituitarism is unlikely. The lower relative frequency of death by external causes might be due to decreased physical and social activity in male subjects with hypopituitarism. Unexpectedly, there were no deaths by suicide, although an impaired quality of life including a reduced sense of well-being has been reported in patients with hypopituitarism and by GH-deficient adults (6).

Finally, to evaluate the findings obtained in this study we should take careful precautions against possible bias. First, the subjects of our study were all selected from those subjected to autopsy. Since all subjects were not submitted to dissection, there may be some bias in the selection of subjects for this study. Secondly, the data were analyzed on the basis of written diagnoses in case records, and clinical and endocrine data were not available. Endocrine status is most important since a recent report indicates that gonadotropin deficiency, if untreated, worsens prognosis (5) and much evidence suggests an association between GH deficiency and cardiovascular dysfunctions or atherosclerosis (6–12). Thirdly, the number of subjects enrolled in this study may have been statistically minimal. Nevertheless, the cause of death among subjects was substantially robust for a sample drawn from pathological examination at autopsy, providing clinically relevant information for the long-term care of patients with hypopituitarism.

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