Excess morbidity and mortality in patients with craniopharyngioma: a hospital-based retrospective cohort study

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Abstract

Objective: Most studies in patients with craniopharyngioma did not investigate morbidity and mortality relative to the general population nor evaluated risk factors for excess morbidity and mortality. Therefore, the objective of this study was to examine excess morbidity and mortality, as well as their determinants in patients with craniopharyngioma.

Design: Hospital-based retrospective cohort study conducted between 1987 and 2014.

Methods: We included 144 Dutch and 80 Swedish patients with craniopharyngioma identified by a computer-based search in the medical records (105 females (47%), 112 patients with childhood-onset craniopharyngioma (50%), 3153 person-years of follow-up). Excess morbidity and mortality were analysed using standardized incidence and mortality ratios (SIRs and SMRs). Risk factors were evaluated univariably by comparing SIRs and SMRs between non-overlapping subgroups.

Results: Patients with craniopharyngioma experienced excess morbidity due to type 2 diabetes mellitus (T2DM) (SIR: 4.4, 95% confidence interval (CI): 2.8–6.8) and cerebral infarction (SIR: 4.9, 95% CI: 3.1–8.0) compared to the general population. Risks for malignant neoplasms, myocardial infarctions and fractures were not increased. Patients with craniopharyngioma also had excessive total mortality (SMR: 2.7, 95% CI: 2.0–3.8), and mortality due to circulatory (SMR: 2.3, 95% CI: 1.1–4.5) and respiratory (SMR: 6.0, 95% CI: 2.5–14.5) diseases. Female sex, childhood-onset craniopharyngioma, hydrocephalus and tumour recurrence were identified as risk factors for excess T2DM, cerebral infarction and total mortality.

Conclusions: Patients with craniopharyngioma are at an increased risk for T2DM, cerebral infarction, total mortality and mortality due to circulatory and respiratory diseases. Female sex, childhood-onset craniopharyngioma, hydrocephalus and tumour recurrence are important risk factors.

European Journal of
Endocrinology
(2018) **178**, 93–102

Introduction

Craniopharyngiomas are benign epithelial tumours located in the (supra)sellar area of the skull that often contain calcifications and fluid-filled cysts. Their locally aggressive behaviour and proximity to critical neurovascular structures (e.g. hypothalamus, pituitary, optic nerves and carotid arteries) characterize them

as challenging tumours (1). Craniopharyngiomas are rare with an estimated incidence rate of 1.7 per million person-years (2). They affect both children and adults, and have peak incidences between 5–9 and 40–44 years of age (3). Craniopharyngiomas are generally treated with neurosurgery, which is sometimes followed by

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radiotherapy (1). Despite encouraging 10-year overall survival rates between 77 and 93% (2, 4, 5, 6, 7), long-term tumour- and treatment-related morbidity is common (2, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14). Hypopituitarism, visual impairment and obesity are the most frequently observed long-term health conditions in patients with craniopharyngioma (6, 7, 8, 9, 10, 11, 14).

Although previous studies have examined morbidity and mortality in patients with craniopharyngioma, only a few investigated morbidity and mortality in relation to the general population. To our knowledge, only one previous study examined excess morbidity (2), and only six previous studies investigated excess mortality in patients with craniopharyngioma relative to a background population (2, 15, 16, 17, 18, 19). The study examining excess morbidity observed significantly increased standardized incidence ratios (SIRs) for type 2 diabetes mellitus (T2DM), fractures, infections, cerebral infarction and visual impairment (2). The studies that investigated excess mortality reported significantly increased standardized mortality ratios (SMRs) for total mortality between 2.5 and 9.3 (2, 15, 16, 17, 18, 19). Many of these studies were limited by a sample size too small to assess cause-specific mortality. The increased risk for morbidity and mortality in patients with craniopharyngioma is likely to be multifactorial, and includes tumour- and treatment-related damages of critical neurovascular structures, as well as their associated health conditions. To date, only three previous studies reported risk factors for excess morbidity and mortality in patients with craniopharyngioma (2, 15, 17). These studies evaluated only a few potential risk factors but identified female sex, childhood-onset disease and panhypopituitarism as significant determinants of excess morbidity and mortality.

The objective of our study was to examine morbidity and mortality in patients with craniopharyngioma in relation to the general population. In addition, the objective was to identify risk factors for excess morbidity and mortality in patients with craniopharyngioma.

Subjects and methods

Study population

We performed a hospital-based retrospective cohort study with data from patients treated for craniopharyngioma at the Erasmus University Medical Centre (Rotterdam, The Netherlands) and the Sahlgrenska University Hospital (Gothenburg, Sweden). We conducted our study between 1987 and 2014 because Swedish general population data

on morbidity and mortality were only available for this period. To increase the strength of our study, we also included patients with craniopharyngioma treated before 1987. These patients entered the study on 1st January 1987. A computer-based search in the medical records identified 224 patients with craniopharyngioma (144 Dutch and 80 Swedish patients) of whom 53 patients (24%) were treated before 1987. The local institutional review board of the Erasmus University Medical Centre and the regional ethical review board in Gothenburg, Sweden, approved this study. All patients gave their informed consent.

Morbidity and mortality

Data on morbidity and mortality in patients with craniopharyngioma were collected from the medical records. Data on mortality from the Dutch general population were derived from Statistics Netherlands, whereas data on morbidity and mortality from the Swedish general population from the Swedish National Patient Registry, the Swedish Cancer Registry and the Swedish National Cause of Death Registry. Data on morbidity from the Dutch general population were unavailable. Therefore, we used Swedish general population data to examine excess morbidity in Dutch patients with craniopharyngioma. Morbidity and cause-specific mortality were categorized according to the International Classification of Diseases, Tenth Revision (ICD-10) (Supplementary data, see section on supplementary data given at the end of this article). Malignant neoplasms, T2DM, myocardial infarction, cerebral infarction and fractures were studied as morbidities. Cause-specific mortality was studied for circulatory diseases (ICD-10 chapter 9) and respiratory diseases (ICD-10 chapter 10). In addition, cause-specific mortality was examined for a few particular conditions (i.e. malignant neoplasms, ischaemic heart disease and cerebrovascular disease). Baseline, tumour and treatment characteristics, as well as craniopharyngioma recurrence, panhypopituitarism and weight status at last available follow-up visit were studied as risk factors for excess morbidity and mortality. Hypothalamic damage was defined as tumour- and/or treatment-related injury to the hypothalamus and/or third ventricle as documented in neuroimaging and/or neurosurgery reports. Craniopharyngioma recurrence was defined as reappearance or re-growth of the tumour after prior treatment. Panhypopituitarism was diagnosed based on formal pituitary function testing in all patients. Weight status was classified as obese (i.e. body mass index $\geq 30 \text{ kg/m}^2$) and non-obese (i.e. body mass index $< 30 \text{ kg/m}^2$).

Statistical analysis

Morbidity and mortality were studied as events and compared between patients with craniopharyngioma and the general population using SIRs and SMRs. SIRs and SMRs were calculated as the ratio of the observed to the expected number of events encountered during the study period, as measured in person-years. Corresponding 95% confidence intervals (CIs) were calculated assuming a Poisson distribution of the observed number of events. Person-years were calculated from the date of study entry to the date of an event or end of study (i.e. 31st December 2014). General population data stratified according to sex, five-year age group and one-year calendar period were used to calculate the expected number of events. SIRs were calculated depending on whether the patient was diagnosed with a specific morbidity on an yearly basis, except for the diagnosis of T2DM, which was assessed at the first event only. SIRs and SMRs were not calculated in case less than three events were observed. Risk factors for excess morbidity and mortality were evaluated univariably by comparing SIRs and SMRs between non-overlapping subgroups (20). Relevant comparisons were also conducted with the exclusion of patients who died within the first six months after their initial craniopharyngioma treatment to account for survivorship bias. A P -value <0.05 was considered statistically significant. Statistical analyses were conducted using SPSS (version 24) and Stata (version 14).

Results

Patient characteristics

We included 224 patients with craniopharyngioma (105 females (47%)) (Table 1). Craniopharyngiomas presented <18 years of age (i.e. childhood-onset) in 112 patients (50%). Patients were followed-up for a median period of 13 years (interquartile range: 6–21), representing 3153 person-years. Median age at the end of study was 42 years (interquartile range: 27–59). Growth hormone replacement therapy was used by 78% of the patients with growth hormone deficiency. Sex steroid replacement therapy was used by 92% of males and premenopausal females with hypogonadotropic hypogonadism. In patients with secondary adrenal insufficiency, the median daily hydrocortisone equivalent dose was 20 mg (interquartile range 20–22.5). Patient characteristics were similar in females compared to males, except for hypertension (51% vs 33%; $P<0.05$) and dyslipidaemia (29% vs 16%; $P<0.05$).

Excess morbidity

Excess morbidity and their risk factors in patients with craniopharyngioma are shown in Fig. 1 and Table 2, respectively. Twenty patients with craniopharyngioma were diagnosed with T2DM compared to the expected number of 4.6, resulting in a significantly increased SIR of 4.4 (95% CI: 2.8–6.8). The excess risk for T2DM was significantly higher in patients with female sex, childhood-onset craniopharyngioma, hydrocephalus, hypothalamic damage, incomplete tumour resection, radiotherapy, tumour recurrence, panhypopituitarism and obesity. We also observed a significantly increased risk for cerebral infarction in patients with craniopharyngioma (SIR: 4.9, 95% CI: 3.1–8.0). The excess risk for cerebral infarction was significantly higher in patients with female sex, childhood-onset craniopharyngioma, hydrocephalus and tumour recurrence. Patients with craniopharyngioma had no increased risk for malignant neoplasms, myocardial infarction or fractures.

Excess morbidity was similar in patients treated before and after 1987, except for T2DM (SIR: 1.8 vs 5.9; $P<0.05$) and fractures (SIR: 2.2 vs 0.7; $P<0.05$). There was no difference in excess morbidity between Dutch and Swedish patients (Supplementary Table 1). To account for survivorship bias, we also evaluated radiotherapy, tumour recurrence, panhypopituitarism and obesity as risk factors for excess morbidity after the exclusion of patients who died within the first six months after their initial craniopharyngioma treatment (i.e. three patients). This did not significantly affect the results (Supplementary Table 2).

Excess mortality

Excess mortality and risk factors for excess total mortality in patients with craniopharyngioma are shown in Fig. 1 and Table 3, respectively. There were 34 observed deaths in patients with craniopharyngioma compared to 12.4 expected, resulting in a significantly increased SMR for total mortality of 2.7 (95% CI: 2.0–3.8). The risk for excess total mortality was significantly higher in females compared to males (SMR: 5.3 vs 1.8; $P<0.05$), patients with childhood-compared to adult-onset craniopharyngioma (SMR: 9.0 vs 1.9; $P<0.05$), patients with compared to without hydrocephalus (SMR: 10.5 vs 1.8; $P<0.05$), patients with compared to without tumour recurrence (SMR: 5.1 vs 1.6; $P<0.05$) and patients with compared to without panhypopituitarism (SMR 4.3 vs 2.0; $P<0.05$). There was no difference in excess total mortality between patients treated before and after 1987. In addition, excess total mortality was similar in Dutch and Swedish patients (Supplementary

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Table 1 Patient characteristics.^a

	All patients (n = 224)	Females (n = 105)	Males (n = 119)
Baseline characteristics			
Age at presentation (years) ^b	20 (9–42)	20 (10–41)	20 (8–42)
Childhood-onset (n (%))	112 (50)	53 (50)	59 (50)
Adult-onset (n (%))	112 (50)	42 (40)	60 (50)
Follow-up (years) ^b	13 (6–21)	14 (7–22)	12 (6–21)
Age at end of study (years) ^b	42 (27–59)	42 (27–57)	41 (26–60)
Tumour characteristics			
Location (n (%))			
Intrasellar	5 (2)	1 (1)	4 (4)
Suprasellar	87 (41)	40 (40)	47 (42)
Intra-/suprasellar	120 (57)	58 (59)	62 (55)
Hydrocephalus (n (%))	62 (28)	32 (31)	30 (26)
Hypothalamic damage (n (%))	90 (43)	43 (43)	47 (43)
Craniopharyngioma treatment			
Neurosurgery (n (%))	210 (94)	99 (94)	111 (93)
Complete resection	69 (39)	30 (36)	39 (42)
Incomplete resection	106 (61)	53 (64)	53 (58)
Radiotherapy (n (%))	101 (45)	48 (46)	53 (45)
Recurrence (n (%))	89 (40)	45 (43)	44 (38)
Long-term health conditions			
Pituitary hormone deficiencies (n (%))	215 (96)	100 (95)	115 (97)
GH	180 (83) ^e	85 (82)	95 (83)
GH dose (mg/day) ^b	0.4 (0.3–0.8)	0.5 (0.3–0.8)	0.4 (0.3–0.7)
FSH/LH	183 (85) ^f	86 (86)	97 (84)
TSH	202 (91) ^g	92 (89)	110 (92)
ACTH	183 (82) ^g	83 (79)	100 (84)
HC equivalent dose (mg/day) ^b	20 (20–22.5)	20 (16–20)	20 (20–25)
ADH	141 (63) ^g	69 (66)	72 (61)
Panhypopituitarism	114 (51)	58 (55)	56 (48)
Visual impairment (n (%)) ^c	156 (77)	72 (76)	84 (79)
Obesity (n (%))	101 (50)	52 (54)	49 (47)
Hypertension (n (%))	76 (41)	44 (51)	32 (33)
Dyslipidaemia (n (%)) ^d	47 (22)	28 (29)	19 (16)

^aEvaluations were based on the number of patients with available data; ^bmedian (interquartile range); ^cdefined as a decreased visual acuity after correction for refraction disorder and/or as the presence of a visual field defect; ^ddefined as the use of lipid-lowering drugs; ^egrowth hormone replacement therapy was used by 141 patients with growth hormone deficiency (78%); ^fsex steroid replacement therapy was used by 143 patients with hypogonadotropic hypogonadism (92% of males and premenopausal females); ^gall patients used hormone replacement therapy. ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; FSH/LH, follicle stimulating hormone/luteinizing hormone; GH, growth hormone; HC, hydrocortisone; mg, milligrams; n, number; TSH, thyroid stimulating hormone.

Table 1). The exclusion of the patients who died within the first six months after their initial craniopharyngioma treatment did not significantly affect the results on risk factors for excess total mortality (**Supplementary Table 2**).

In the analyses on cause-specific mortality, we observed a significantly increased risk for mortality due to circulatory diseases (ICD-10 chapter 9) (SMR: 2.3, 95% CI: 1.1–4.5) and respiratory diseases (ICD-10 chapter 10) (SMR: 6.0, 95% CI: 2.5–14.5). The excess risk for mortality due to circulatory diseases was mainly due to cerebrovascular disease. We observed no excess mortality due to malignant neoplasms and ischaemic heart disease. The low number of observed deaths precluded the reliable assessment of determinants of cause-specific mortality. Individual causes of death in patients with craniopharyngioma are shown in **Supplementary Table 3**.

Discussion

In this large hospital-based retrospective cohort study, we investigated excess morbidity and mortality in 224 patients with craniopharyngioma after 3153 person-years of follow-up. We observed patients with craniopharyngioma to be at a significantly increased risk for T2DM, cerebral infarction, total mortality and mortality due to circulatory and respiratory diseases relative to the general population. The excess risk for mortality due to circulatory diseases was mainly due to a high cerebrovascular mortality. We identified female sex, childhood-onset craniopharyngioma, hydrocephalus, hypothalamic damage, incomplete tumour resection, radiotherapy, tumour recurrence, panhypopituitarism and obesity as significant risk factors for excess morbidity and mortality in a series of univariable analyses.

Figure 1

Excess morbidity and mortality in patients with craniopharyngioma. (A) Morbidity. (B) Mortality. *Observed malignant neoplasms included breast cancer ($n=1$), malignant brain tumour ($n=1$), melanoma ($n=1$), mesothelioma ($n=1$), neuro-endocrine tumour of the appendix ($n=1$), ovarian cancer ($n=1$), pancreatic cancer ($n=1$), prostate cancer ($n=3$). CI, confidence interval; E, expected; O, observed; SIR, standardized incidence ratio; SMR, standardized mortality ratio; T2DM, type 2 diabetes mellitus.

Similar to our study, some previous studies investigated morbidity and mortality in patients with craniopharyngioma relative to the general population (Table 4) (2, 15, 16, 17, 18, 19). The results of these studies are in concordance with our findings regarding the significantly increased risk for T2DM, cerebral infarction, total mortality and mortality due to circulatory and respiratory diseases in patients with craniopharyngioma. The increased risk for circulatory diseases in patients with craniopharyngioma seems to be mainly due to an adverse metabolic profile associated with hypothalamic damage and hypopituitarism (14, 21). Hypothalamic damage may result in acquired leptin and insulin resistance, as well as autonomic nervous system dysfunction, which may altogether promote the development of obesity and its associated metabolic derangements (22). The adverse metabolic profile associated with hypopituitarism may be due to inadequately treated pituitary hormone deficiencies, as well as to currently available hormone replacement regimens that do not appropriately simulate hypothalamic-pituitary physiology (23, 24, 25). The increased risk for

respiratory mortality has also been observed in patients with hypopituitarism due to other causes (4), and is likely to be due to an increased incidence of severe respiratory tract infections. Secondary adrenal insufficiency and glucocorticoid replacement therapy, as well as immune dysfunction associated with other pituitary hormone deficiencies seem to be responsible for an increased infection risk in patients with hypopituitarism (26). In our study, all patients who died from respiratory diseases suffered from secondary adrenal insufficiency. In these patients, fatal events were probably at least partly due to adrenal crises related to secondary adrenal insufficiency. This is supported by Burman *et al.* who found that adrenal crises in response to acute stress and intercurrent illness contribute to the death of adult patients with hypopituitarism (27). Patients with craniopharyngioma seem to be at an increased risk for mortality compared to patients with hypopituitarism due to other causes (4). This may be due to craniopharyngioma-specific factors, like a locally aggressive tumour behaviour, a high recurrence rate, severe hypopituitarism and a high frequency of hypothalamic damage.

We identified female sex, childhood-onset disease, hydrocephalus, tumour recurrence and panhypopituitarism as the most important risk factors for excess morbidity and mortality in patients with craniopharyngioma in a series of univariable analyses. Although previous studies evaluated only a few potential determinants of excess morbidity and mortality in patients with craniopharyngioma, some of them also observed a significantly increased risk for excess morbidity and mortality associated with female sex, childhood-onset craniopharyngioma and panhypopituitarism (2, 15, 17). The reason for the increased morbidity and mortality in female patients compared to male patients with craniopharyngioma is unknown, but sex-specific factors associated with hypopituitarism and its management are likely to be involved (4). This is illustrated by studies in patients with hypopituitarism due to various causes that also observed a significantly increased risk for excess mortality associated with female sex (28). Nielsen *et al.* suggested that pituitary hormone deficiencies may be underdiagnosed in females compared to males due to the absence of sex-specific diagnostic tests (29). In their study, they observed a substantially lower prevalence of pituitary hormone deficiencies in female patients compared to male patients after surgery for nonfunctioning pituitary adenoma. In addition, Erfurth *et al.* reported a significantly longer duration of untreated hypopituitarism in female (but not in male) patients with pituitary tumours (including craniopharyngioma) who died of cerebrovascular disease (30). Moreover, some studies suggested that sex-specific

Table 2 Risk factors for excess morbidity in patients with craniopharyngioma.

Risk factors	Malignant neoplasms		T2DM		Myocardial infarction		Cerebral infarction		Fractures	
	SIR (95% CI)	P	SIR (95% CI)	P	SIR (95% CI)	P	SIR (95% CI)	P	SIR (95% CI)	P
Sex										
Female	1.1 (0.4–2.5)	0.62	7.3 (3.9–13.5)	<0.05	3.4 (1.1–10.5)	0.11	8.1 (4.1–16.2)	<0.05	1.7 (0.8–3.5)	0.31
Male	0.8 (0.3–1.8)		3.1 (1.7–5.8)		1.0 (0.4–2.7)		3.7 (1.9–7.1)		1.0 (0.5–2.0)	
Onset										
Childhood	NC	NC	10.7 (5.4–21.4)	<0.05	NC	NC	16.0 (6.7–38.4)	<0.05	1.3 (0.6–2.8)	0.76
Adult	0.8 (0.4–1.7)		3.1 (1.8–5.5)		1.4 (0.6–3.1)		3.8 (2.2–6.8)		1.1 (0.5–2.4)	
Hydrocephalus										
Yes	NC	NC	10.1 (4.5–22.4)	<0.05	NC	NC	14.6 (6.6–32.5)	<0.05	1.2 (0.4–3.8)	1.00
No	0.9 (0.4–1.7)		3.7 (2.2–6.3)		1.2 (0.5–3.0)		3.9 (2.1–7.0)		1.2 (0.7–2.3)	
Hypothalamic damage										
Yes	0.9 (0.3–2.9) ^a	1.00	8.4 (4.3–16.1) ^b	<0.05	2.3 (0.7–7.0) ^d	0.32	5.5 (2.5–12.3) ^f	0.83	NC	NC
No	0.9 (0.4–1.9)		3.3 (1.8–6.2)		1.0 (0.3–3.2)		4.9 (2.6–9.0)		1.8 (1.0–3.2)	0.54
Resection										
Complete	1.7 (0.7–4.0) ^a	0.18	2.6 (1.0–6.9) ^c	<0.05	NC ^e	NC	4.7 (2.0–11.4) ^g	0.97	0.8 (0.3–2.4) ^h	0.34
Incomplete	0.7 (0.3–2.0)		7.1 (4.2–11.9)		2.1 (0.8–5.7)	0.47	4.8 (2.3–10.0)		1.2 (0.6–2.7)	
Radiotherapy										
Yes	1.2 (0.5–2.7)	0.32	6.8 (4.0–11.5)	<0.05	1.9 (0.7–5.0)		4.9 (2.3–10.2)	0.97	0.9 (0.4–2.2)	NC
No	0.6 (0.2–1.7)		2.4 (1.1–5.3)		1.1 (0.4–3.5)	0.33	5.0 (2.7–9.3)	<0.05	1.5 (0.8–2.8)	
Recurrence										
Yes	1.1 (0.4–2.8)	0.61	6.5 (3.5–12.2)	<0.05	2.0 (0.6–6.1) ^d		8.0 (4.2–15.3) ^f		NC ⁱ	0.75
No	0.8 (0.4–1.8)		3.3 (1.8–6.2)		0.9 (0.3–2.8)	0.45	3.0 (1.5–6.4)	0.29	1.1 (0.5–2.4)	0.48
Panhypopituitarism										
Yes	0.7 (0.2–2.2)	0.62	7.3 (4.1–12.8)	<0.05	2.1 (0.7–6.4)	NC	6.9 (3.3–14.4)	0.70	1.3 (0.7–2.7)	<0.05
No	1.0 (0.5–2.1)		2.7 (1.4–5.5)		1.2 (0.5–3.2)		4.1 (2.2–7.7)		1.0 (0.4–2.3) ⁱ	
Obesity										
Yes	0.6 (0.2–1.9) ^a	0.46	8.8 (5.3–14.7)	<0.05	2.4 (0.9–6.3) ^d		5.6 (2.7–11.8) ^f	0.94	1.5 (0.7–2.9)	
No	1.0 (0.5–2.3)		1.9 (0.8–4.7)		NC		4.6 (2.4–8.8)		2.2 (1.1–4.2)	
Treated										
<1987	0.8 (0.2–2.4)	0.76	1.8 (0.6–5.5)	<0.05	2.1 (0.7–6.7)	0.47	4.8 (1.8–12.7)		0.7 (0.3–1.6)	
≥1987	1.0 (0.5–2.0)		5.9 (3.7–9.5)		1.2 (0.4–3.1)		5.0 (2.9–8.6)			

^aData missing in one patient with a malignant neoplasm; ^bdata missing in one patient with T2DM; ^cdata missing in two patients with T2DM; ^ddata missing in one patient with a myocardial infarction; ^edata missing in two patients with a myocardial infarction; ^fdata missing in one patient with a cerebral infarction; ^gdata missing in five patients with a cerebral infarction; ^hdata missing in five patients with a fracture; ⁱdata missing in one patient with a fracture.

CI, confidence interval; NC, not calculated; P, P-value; SIR, standardized incidence ratio; T2DM, type 2 diabetes mellitus.

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Table 3 Risk factors for excess total mortality in patients with craniopharyngioma.

Risk factors	Observed	Expected	SMR	95% CI	P value
Sex					
Female	18	3.4	5.3	3.3–8.4	<0.05
Male	16	9.0	1.8	1.1–2.9	
Onset					
Childhood	13	1.4	9.0	5.3–15.6	<0.05
Adult	21	11.0	1.9	1.2–2.9	
Hydrocephalus					
Yes	15	1.4	10.5	6.3–17.4	<0.05
No	19	10.5	1.8	1.2–2.8	
Hypothalamic damage ^a					
Yes	16	4.3	3.7	2.3–6.0	0.12
No	15	6.9	2.2	1.3–3.6	
Resection					
Complete ^b	6	3.5	1.7	0.8–3.9	0.15
Incomplete	16	5.0	3.2	2.0–5.2	
Radiotherapy					
Yes	15	4.8	3.1	1.9–5.2	0.53
No	19	7.6	2.5	1.6–3.9	
Recurrence					
Yes ^c	19	3.7	5.1	3.3–8.0	<0.05
No	14	8.7	1.6	1.0–2.7	
Panhypopituitarism					
Yes ^c	15	3.5	4.3	2.6–7.1	<0.05
No	18	8.9	2.0	1.3–3.2	
Obesity					
Yes ^d	14	4.2	3.3	2.0–5.6	0.08
No	13	7.5	1.7	1.0–3.0	
Treatment					
<1987	8	3.4	2.4	1.2–4.8	0.64
≥1987	26	9.1	2.9	2.0–4.2	

^aData missing in three patients who died; ^bdata missing in 12 patients who died; ^cdata missing in one patient who died; ^ddata missing in seven patients who died.

CI, confidence interval; SMR, standardized mortality ratio.

differences in the pathophysiological states associated with pituitary hormone deficiencies and effects of currently available hormone replacement regimens contribute to the increased morbidity and mortality in female patients compared to male patients with pituitary disease (4, 21, 28).

The increased morbidity and mortality in patients with childhood- compared to adult-onset craniopharyngioma may be explained by tumour characteristics. Wijnen *et al.* reported that patients with childhood-onset disease present significantly more multicystic tumours, as well as tumours associated with hydrocephalus and hypothalamic damage compared to patients with adult-onset disease (7). Tumour characteristics may also explain the significantly increased risk for excess morbidity and mortality associated with hydrocephalus and tumour recurrence. Large and aggressive craniopharyngiomas that cause hydrocephalus and tend to recur after treatment may induce more tumour- and treatment-related brain damage, thereby increasing the risk for excess morbidity and mortality.

Radiotherapy is an important risk factor for cerebrovascular disease (31). Interestingly, we observed an equal excess risk for cerebral infarction in patients treated with and without radiotherapy. This indicates that other factors, like neurosurgery and an adverse metabolic profile associated with hypothalamic damage and hypopituitarism, also contribute to the excess risk for cerebral infarction in patients with craniopharyngioma. Additionally, our study population may be too young and our follow-up duration too short to observe an increased risk for cerebral infarction associated with radiotherapy. Previous studies identified an advanced age and a prolonged follow-up duration after radiotherapy as important risk factors for radiation-induced cerebrovascular disease (31). The latter explanation may potentially also apply to the absence of an increased risk for myocardial infarction and malignant neoplasms in patients with craniopharyngioma in our study.

Our study has several strengths. We investigated morbidity and mortality in patients with

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Table 4 Other studies that investigated excess mortality in patients with craniopharyngioma.

References	Country	Setting	Period	n (%)	Median age at craniopharyngioma dx. (range) (years)	Median follow-up (range) (years)	Person-years	SMR for total mortality (95% CI)
(15)	Sweden	Hospital-based	1951–1988	♀ 24 (40) ♂ 36 (60)	28 (3–71)	13 (0–40)	NA	5.6 (3.7–8.2)
(16)	United Kingdom	Hospital-based	1992–2000	♀/♂ 118	NA	NA	NA	9.3 (5.8–14.8)
(17)	The Netherlands	Hospital-based	1965–2002	♀ 30 (55) ♂ 25 (45)	29 (4–74)	10 (1–37)	828	2.9 (1.4–5.0)
(18)	Ireland	Hospital-based	1980–2008	♀ 31 (44) ♂ 39 (56)	28 (0–80)	8 (1–50)	NA	8.8 (5.4–13.3)
(19)	KIMS-database ^a	Hospital-based	1994–2011	♀/♂ 1562	NA	NA	8392	2.5 (1.9–3.1)
(2)	Sweden	Population-based	1987–2011	♀ 156 (51) ♂ 151 (49)	35 (0–81) ^b	9 (0–25) ^c	2882	3.8 (2.9–5.0)
This study	The Netherlands and Sweden	Hospital-based	1987–2014	♀ 105 (47) ♂ 119 (43)	20 (9–42) ^c	13 (6–21) ^d	3153	2.7 (2.0–3.8)

^aPfizer International Metabolic Database; ^bmean (range); ^cmedian (interquartile range).

♀, female; ♂, male; CI, confidence interval; dx., diagnosis; n, number; NA, not available; SMR, standardized mortality ratio.

craniopharyngioma relative to the general population. Additionally, we studied a large number of potential risk factors for excess morbidity and mortality. Furthermore, through international collaboration, we could establish a large cohort of both patients with childhood- and adult-onset craniopharyngioma. The international collaboration also enabled us to replicate our findings in two study populations. Despite these strengths, some limitations of our study should be discussed. The (tertiary) hospital-based setting may induce selection bias of patients with more advanced disease. Additionally, we included patients with craniopharyngioma treated before 1987, which increased the size of our study population and thereby the strength of our analyses, but may have also induced a survivorship bias. However, when we analysed this issue, we did not find any survivorship bias, except for T2DM. This indicates that the true excess risk for T2DM might be even higher than SIR: 4.4 (95% CI: 2.8–6.8). Another limitation of our study is the use of Swedish general population data to calculate SIRs in Dutch patients with craniopharyngioma. Although the Swedish general population has been reported to be slightly healthier than the Dutch general population, the difference is minimal (32). An additional limitation of our study is that we defined hypothalamic damage based on data reported in the medical records. Recently, several neuroradiological grading systems for craniopharyngioma-related hypothalamic damage have been developed (33, 34, 35, 36). Mortini *et al.* validated some of these classification systems regarding their correlation with obesity (37). Unfortunately, due to the retrospective design of our study, we were unable to use these classification systems. Future studies are needed to validate these grading systems and to investigate their correlation with other symptoms of hypothalamic damage. Furthermore, in our study, data on lifestyle factors and the histological subtype of craniopharyngioma were unavailable. Another limitation of our study is that the cause of death was unknown in seven patients with craniopharyngioma. Although this did not affect the SMR for total mortality, the cause-specific SMRs could have been underestimated. Since many patients with craniopharyngioma suffer from growth hormone deficiency and secondary adrenal insufficiency (7), and since these conditions are known to be associated with excess circulatory and respiratory mortalities (4), it is tempting to speculate that mortality due to circulatory, as well as respiratory diseases may have been underestimated in our study. In addition, a previous study by Burman *et al.* has shown

that deaths due to adrenal crises related to secondary adrenal insufficiency are probably underestimated in patients with hypopituitarism as well (27). Moreover, 67 of the 80 Swedish patients with craniopharyngioma enrolled in our study also took part in a previous study on excess morbidity and mortality in patients with craniopharyngioma (2). This previous population-based study by Olsson *et al.* was a nationwide study that included 307 patients with craniopharyngioma from Sweden. In this study, excess morbidity and mortality were investigated using registry-provided data only. Since the current study used data derived from the medical records to examine excess morbidity and mortality, the results provided in the present study are more accurate and extensive compared to the previous study by Olsson *et al.* (2). We were able to study a relatively large number of new risk factors for excess morbidity and mortality. In addition, the follow-up duration in the current study is considerably longer compared to the previous study by Olsson *et al.* (i.e. median 13 vs 8 years) (2). Finally, our results on risk factors for excess morbidity and mortality should be interpreted cautiously because many determinants of excess morbidity and mortality in patients with craniopharyngioma are interrelated (e.g. radiotherapy, hypothalamic damage, panhypopituitarism and obesity).

In conclusion, we observed patients with craniopharyngioma to be at significantly increased risk for T2DM, cerebral infarction, total mortality and mortality due to circulatory and respiratory diseases relative to the general population. The excess risk for mortality due to circulatory diseases was mainly due to a high cerebrovascular mortality. We identified female sex, childhood-onset disease, hydrocephalus, tumour recurrence and panhypopituitarism as the most important risk factors for excess morbidity and mortality in patients with craniopharyngioma in a series of univariable analyses. Since excess morbidity and mortality in patients with craniopharyngioma are highly dependent on tumour- and treatment-related hypothalamic-pituitary damage, we advocate individualized treatment strategies that aim to preserve hypothalamic-pituitary function and provide optimal endocrine care.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-17-0707>.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of this study.

Funding

This research did not receive any specific grant from any funding agency in the public, commercial or not-for-profit sector.

Acknowledgements

The authors would like to thank the physicians involved in the treatment and follow-up care of our patients.

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Received 25 August 2017

Revised version received 8 October 2017

Accepted 16 October 2017