The metabolic syndrome and its components in 178 patients treated for craniopharyngioma after 16 years of follow-up

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Abstract

Objective: Patients with craniopharyngioma are at an increased risk for cardio- and cerebrovascular mortality. The metabolic syndrome (MetS) is an important cardiometabolic risk factor, but barely studied in patients with craniopharyngioma. We aimed to investigate the prevalence of and risk factors for the MetS and its components in patients with craniopharyngioma.

Design: Cross-sectional study with retrospective data.

Methods: We studied the prevalence of and risk factors for the MetS and its components in 110 Dutch (median age 47 years, range 18–92) and 68 Swedish (median age 50 years, range 20–81) patients with craniopharyngioma with ≥ 3 years of follow-up (90 females (51%); 83 patients with childhood-onset craniopharyngioma (47%); median follow-up after craniopharyngioma diagnosis 16 years (range 3–62)). In Dutch patients aged 30–70 years and Swedish patients aged 45–69 years, we examined the prevalence of the MetS and its components relative to the general population.

Results: Sixty-nine (46%) of 149 patients with complete data demonstrated the MetS. Prevalence of the MetS was significantly higher in patients with craniopharyngioma compared with the general population (40% vs 26% ($P < 0.05$) for Dutch patients; 52% vs 15% ($P < 0.05$) for Swedish patients). Multivariable logistic regression analysis identified visual impairment as a borderline significant predictor of the MetS (OR 2.54, 95% CI 0.95–6.81; $P = 0.06$) after adjustment for glucocorticoid replacement therapy and follow-up duration. Age, female sex, tumor location, radiological hypothalamic damage, ⁹⁰Yttrium brachytherapy, glucocorticoid replacement therapy and follow-up duration significantly predicted components of the MetS.

Conclusions: Patients with craniopharyngioma are at an increased risk for the MetS, especially patients with visual impairment.

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Introduction

Craniopharyngiomas are (supra)sellar epithelial tumors that often contain calcifications and fluid-filled cysts. Despite their benign histology, they are associated with

significant morbidity due to both tumor and treatment (1). Craniopharyngiomas affect children and adults and are predominantly diagnosed between 5–9 and 40–44 years

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of age (2). They are usually treated with neurosurgical excision with or without postoperative radiotherapy. Other treatment options include the intracystic appliance of beta-emitting isotopes or chemotherapeutic substances, as well as stereotactic radiosurgery (1). Patients with craniopharyngioma are at increased risk for premature mortality (3, 4, 5, 6). The most important cause of premature mortality in patients with craniopharyngioma is cardio- and cerebrovascular disease, with a reported standardized mortality ratio between 3.2 and 19.4 (4, 5, 6). The increased risk for cardio- and cerebrovascular mortality in patients with craniopharyngioma is poorly understood but likely to be multifactorial. Tumor- and treatment-related damage of critical neurovascular structures (e.g. hypothalamus, pituitary, optic nerves and carotid arteries), as well as their associated morbidities with currently available management options (e.g. present hormone replacement regimens for hypopituitarism) may be involved.

Studies in the general population identified the metabolic syndrome (MetS) as an important risk factor for cardio- and cerebrovascular disease, as well as type 2 diabetes mellitus (7). The MetS, which was conceptualized by Reaven in 1988 (8), has been associated with a two-fold increased risk for cardio- and cerebrovascular disease and a five-fold increased risk for type 2 diabetes mellitus (7). During the last two decades, several definitions of the MetS have been proposed (9, 10, 11, 12, 13, 14). All these definitions include obesity, insulin resistance, dyslipidemia and elevated blood pressure as their main components. To date, only a few studies assessed the MetS and its components in patients with craniopharyngioma (15, 16, 17, 18, 19, 20). Small study populations that mainly consist of children, a lack of comparison with the general population and the evaluation of only a few potential risk factors for the MetS and its components are major limitations of these studies.

The objectives of our study were to determine the prevalence of and risk factors for the MetS and its components in patients with craniopharyngioma. In a subset of patients, we examined the prevalence of the MetS and its components in relation to the general population.

Subjects and methods

Study population

Patients treated for craniopharyngioma at the Erasmus University Medical Centre (Rotterdam, the Netherlands) and the Sahlgrenska University Hospital (Gothenburg,

Sweden) were eligible for participation in this cross-sectional study with retrospective data if they were ≥ 18 years of age at their last follow-up visit, had ≥ 3 years of follow-up after craniopharyngioma diagnosis and presented data on ≥ 1 component of the MetS. A computer-based search in the medical records identified 225 patients with craniopharyngioma of whom 178 were eligible (110 Dutch and 68 Swedish patients). Craniopharyngiomas were diagnosed in 83 patients (47%) who were < 18 years of age (i.e. childhood-onset) and in 95 (53%) patients who were ≥ 18 years of age (i.e. adult-onset). All patients gave their informed consent and were included in the study.

In a subset of patients, we examined the prevalence of the MetS, its components and type 2 diabetes mellitus in relation to the general population. This includes Dutch patients aged 30–70 years ($n=73$) and Swedish patients aged 45–69 years ($n=29$). Data from the Dutch general population were reported in the ‘Nederland de Maat Genomen’ (NL de Maat) study (21); data from the Swedish general population in the ‘Life conditions, Stress and Health’ (LSH) study (22). In the ‘NL de Maat’ study, 2059 females and 1806 males from the Dutch general population, aged 30–70 years, were assessed for cardio- and cerebrovascular disease risk factors between 2009 and 2010 (21). The ‘LSH’ study included 505 females and 502 males from the Swedish general population, aged 45–69 years, who were evaluated for cardio- and cerebrovascular disease risk factors between 2003 and 2004 (22). The local institutional review board of the Erasmus University Medical Centre and the regional ethics review board in Gothenburg, Sweden, approved this study.

Data collection

Data on baseline characteristics, tumor characteristics, craniopharyngioma treatment, recurrence and long-term health outcome were collected from the medical records. Craniopharyngioma location, hydrocephalus and radiological hypothalamic damage were studied as tumor characteristics. Location was classified as intrasellar, suprasellar and both intra-/suprasellar. Radiological hypothalamic damage was defined as tumor- and/or treatment-related injury to the hypothalamus and/or third ventricle as visualized on neuroimaging. Neurosurgery, radiotherapy and ^{90}Y trium brachytherapy were studied as craniopharyngioma treatment modalities. Recurrence was defined as reappearance or re-growth of the craniopharyngioma after the prior treatment. The MetS and parameters

Table 1 Definition of the MetS (14).

At least three of the following five criteria:
Body mass index $>30\text{ kg/m}^2$
Fasting glucose $\geq 5.6\text{ mmol/L}$ or drug treatment for increased glucose
Triglycerides $\geq 1.7\text{ mmol/L}$ or drug treatment for elevated triglycerides
HDL cholesterol $<1.0\text{ mmol/L}$ in males and $<1.3\text{ mmol/L}$ in females or drug treatment for reduced HDL cholesterol
Blood pressure $\geq 130/85\text{ mmHg}$ or drug treatment for hypertension

MetS, metabolic syndrome.

reflecting its components (i.e. body mass index, fasting glucose, triglycerides, high-density lipoprotein (HDL) cholesterol, systolic and diastolic blood pressure), presence of and treatment for diabetes mellitus, dyslipidemia, and hypertension, glycated hemoglobin (HbA1c), cardio- and cerebrovascular morbidity, presence of and treatment for hypopituitarism, visual impairment and current treatment for epilepsy and psychiatric illness were studied as conditions reflecting long-term health outcome. The MetS was defined according to the Joint Interim Statement of the International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; World Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity (Table 1) (14). According to this definition, patients are classified as obese if waist circumference is greater than population- and country-specific definitions or if body mass index is $>30\text{ kg/m}^2$. As data on waist circumference were unavailable in our patients, we classified patients as obese by body mass index only. Pituitary hormone deficiencies were diagnosed by formal pituitary function testing in all patients. Based on clinical guidelines and shared decision making growth hormone replacement therapy (GHRT) was started. Sex steroid replacement therapy was discontinued in females when a physiological menopausal age (i.e. approximately 51 years) was reached. Visual impairment was defined as a decreased visual acuity after correction for refraction disorders and/or as the presence of a visual field defect.

Statistical analysis

Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS 24). Evaluations were based on the number of patients with available data. Continuous and categorical variables were compared

using Student's *t*-tests and Chi-square tests respectively. Non-parametric equivalent tests were used when assumptions were not met. Prevalence of the MetS, its components and type 2 diabetes mellitus were compared between patients with craniopharyngioma and the general population using one-sample proportion tests. Logistic regression analyses were performed to identify risk factors for the MetS and its components. Age, sex, age group at craniopharyngioma diagnosis, tumor location, hydrocephalus, radiological hypothalamic damage, radiotherapy, $^{90}\text{Yttrium}$ brachytherapy, craniopharyngioma recurrence, panhypopituitarism, treatment of growth hormone deficiency (GHD), hypogonadotropic hypogonadism, secondary adrenal insufficiency, secondary hypothyroidism and diabetes insipidus, as well as visual impairment and treatment for epilepsy and psychiatric illness were evaluated as potential risk factors. Variables statistically significant in univariable regression (i.e. a *P* value <0.05 (two-tailed)) were further evaluated by multivariable regression. All multivariable regression analyses were adjusted for follow-up duration.

Results

Patient characteristics

We evaluated 178 patients (90 females (51%)) with craniopharyngioma (Table 2). Median follow-up after craniopharyngioma diagnosis was 16 years (range 3–62). Median age at last follow-up assessment was 47 years (range 18–92) (i.e. median 47 years (range 18–92) in Dutch patients, and median 50 years (range 20–81) in Swedish patients). Patient characteristics were similar in females and males, except for secondary hypothyroidism (88% vs 97%; $P<0.05$). GHRT was used by 117 (79%) patients with GHD. Thirty-five (30%) of these patients used GHRT during childhood. Sex steroid replacement therapy was used by 122 (95% of males and premenopausal females) patients with hypogonadotropic hypogonadism. All premenopausal females on sex steroid replacement therapy used regular oral estrogen–progestin replacement regimens. Three males did not use sex steroid replacement therapy due to prostate cancer. All patients with secondary adrenal insufficiency, secondary hypothyroidism and diabetes insipidus were adequately treated with hormone replacement therapy. Glucocorticoid replacement therapy was used by 145 (82%) patients. The median daily hydrocortisone equivalent dose in these patients was 20mg (range 5–50). Antiepileptic drugs were used by 15 (8%) patients; psychiatric drugs (i.e. antipsychotics,

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Table 2 Patient characteristics.

	All craniopharyngiomas (n=178)	Females (n=90)	Males (n=88)
Baseline characteristics			
Age at diagnosis (years) ^a	23 (0–79)	23 (4–73)	24 (0–79)
Childhood-onset (n (%))	83 (47)	40 (44)	43 (49)
Adult-onset (n (%))	95 (53)	50 (56)	45 (51)
Follow-up since diagnosis (years) ^a	16 (3–62)	16 (3–62)	18 (3–48)
Age at last follow-up assessment (years) ^a	47 (18–92)	48 (18–82)	47 (18–92)
Tumor characteristics			
Location (n (%))			
Intrasellar	4 (2)	1 (1)	3 (4)
Suprasellar	67 (40)	34 (41)	33 (40)
Intra-/suprasellar	95 (57)	49 (58)	46 (52)
Hydrocephalus (n (%))	47 (27)	26 (29)	21 (24)
Radiological hypothalamic damage (n (%))	65 (39)	31 (37)	34 (42)
Craniopharyngioma treatment			
Neurosurgery (n (%))	165 (93)	84 (93)	81 (92)
Radiotherapy (n (%))	85 (48)	43 (48)	42 (48)
⁹⁰ Yttrium brachytherapy (n (%))	29 (16)	16 (18)	13 (15)
Recurrence (n (%))	70 (40)	36 (40)	34 (40)
Long-term health outcome			
Pituitary hormone deficiencies (n (%))			
GH	148 (85) ^b	73 (82)	75 (88)
FSH/LH	155 (88) ^c	76 (84)	79 (91)
ACTH	145 (82) ^d	69 (77)	76 (86)
TSH	163 (92) ^d	78 (88)	85 (97)
ADH	111 (62) ^d	55 (61)	56 (64)
Panhypopituitarism	93 (53)	46 (51)	47 (54)
Visual impairment (n (%))	126 (78)	63 (77)	63 (80)
Body mass index (kg/m ²) ^a	30.1 (16.9–59.5)	30.4 (20.3–59.5)	30.1 (16.9–49.1)
Treatment for epilepsy (n (%))	15 (8)	5 (6)	10 (11)
Treatment for psychiatric illness (n (%))	24 (14)	11 (13)	13 (15)

^aMedian (range). ^bGHRT was used by 117 patients with GHD (79%). ^cSex steroid replacement therapy was used by 122 patients with hypogonadotropic hypogonadism (95% of males and premenopausal females). ^dAll patients were adequately treated with hormone replacement therapy. ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; FSH/LH, follicle stimulating hormone/luteinizing hormone; GH, growth hormone; GHD, growth hormone deficiency; GHRT, growth hormone replacement therapy; kg/m², kilograms per square meter; n, number; TSH, thyroid-stimulating hormone.

antidepressants, or benzodiazepines) by 24 (14%) patients. One patient was known with type 1 diabetes mellitus; another patient had gestational diabetes. These two patients were excluded from the analyses on the MetS and its components.

Patient characteristics in Dutch compared with Swedish patients with craniopharyngioma, patients with childhood-onset compared with adult-onset craniopharyngioma, patients with treated compared with untreated GHD and patients with obesity compared to patients without obesity are shown in [Supplementary Table 1](#) (see section on [supplementary data](#) given at the end of this article).

The MetS and its components

In our study, 69 (46%) of 149 patients with complete data demonstrated the MetS ([Table 3](#)). Twenty patients (29%) had three components of the MetS, 30 (43%) patients had four components and 14 (20%) patients had

five components. In 5 (7%) patients with the MetS the exact number of components was unknown. Obesity was present in 84 (52%) patients. Increased fasting glucose affected 57 (37%) patients; elevated triglycerides 80 (54%) patients. Reduced HDL cholesterol was found in 65 (46%) patients; and elevated blood pressure in 96 (56%) patients. In the subset of patients who were compared with the general population (i.e. Dutch patients aged 30–70 years and Swedish patients aged 45–69 years), prevalence of the MetS was significantly higher in patients with craniopharyngioma (40% vs 29% ($P<0.05$) for Dutch patients; 52% vs 15% ($P<0.05$) for Swedish patients). Prevalence of obesity, reduced HDL cholesterol and elevated blood pressure were also significantly higher in Dutch and Swedish patients with craniopharyngioma compared with the general population. Prevalence of elevated triglycerides could only be compared with the general population in Swedish patients with craniopharyngioma. In this subgroup, prevalence of

Table 3 The MetS, its components, type 2 diabetes mellitus, and cardio- and cerebro-vascular morbidity in patients with craniopharyngioma.

	Comparison of craniopharyngioma patients with general population				
	Patients with craniopharyngioma		General population (21)		P value
	Dutch patients ^c	Swedish patients ^d	General population (22)	Dutch vs Swedish patients	
MetS and its components					
MetS	69/149 (46%)	22/55 (40%)	29%	15/29 (52%)	<0.05
Obesity	84/162 (52%)	34/63 (54%)	13%	14/28 (50%)	<0.05
Increased fasting glucose	57/156 (37%)	13/61 (21%)	NA	15/29 (52%)	NA
Elevated triglycerides	80/149 (54%)	27/56 (48%)	NA	18/29 (62%)	<0.05
Reduced HDL cholesterol	65/141 (46%)	18/51 (35%)	6%	16/29 (55%)	<0.05
Elevated blood pressure	96/172 (56%)	44/69 (64%)	31%	15/29 (52%)	<0.05
Type 2 diabetes mellitus and cardio- and cerebro-vascular morbidity					
Type 2 diabetes mellitus	24/178 (14%)	8/73 (11%)	5%	5/29 (17%)	<0.05
HbA1c (mmol/mol) ^{a,b}	34 (23–80)	36 (22–69)	NA	36 (29–77)	NA
Myocardial infarction	6/178 (3%)	4/73 (6%)	NA	0/29 (0%)	NA
Cerebrovascular accident	15/178 (8%)	4/73 (6%)	NA	1/29 (3%)	NA

^aMedian (range). ^bData available in 118 patients. ^cSubset of Dutch patients aged 30–70 years. ^dSubset of Swedish patients aged 45–69 years. HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; MetS, metabolic syndrome; NA, not available.

elevated triglycerides was significantly higher in patients with craniopharyngioma (Table 3).

Prevalence of the MetS and its components were similar in Dutch and Swedish patients with craniopharyngioma, except for increased fasting glucose, which was significantly more common in Swedish compared with Dutch patients (47% vs 29%; $P<0.05$) (Table 3). Female patients had a significantly higher prevalence of reduced HDL cholesterol (58% vs 35%; $P<0.05$) and elevated blood pressure (64% vs 47%; $P<0.05$) compared with male patients. Elevated blood pressure was significantly more common in patients with adult-onset compared with childhood-onset craniopharyngioma (64% vs 46%; $P<0.05$). There were no significant differences in the MetS and its components between patients with treated and untreated GHD (Table 4).

Risk factors for the MetS and its components in patients with craniopharyngioma

Results of the univariable and multivariable logistic regression analyses on risk factors for the MetS are shown in Table 5. Glucocorticoid replacement therapy (OR: 3.27, 95% CI: 1.22–8.74; $P<0.05$) and visual impairment (OR: 2.63, 95% CI: 1.11–6.24; $P<0.05$) were identified as significant risk factors for the MetS in the univariable analyses. In the multivariable analysis, visual impairment was borderline significantly associated with the MetS (OR: 2.54, 95% CI: 0.95–6.81; $P=0.06$) after adjustment for glucocorticoid replacement therapy and follow-up duration. Radiological hypothalamic damage was identified as a significant risk factor for obesity (OR: 9.86, 95% CI: 1.59–61.1; $P<0.05$) after adjustment for age, ⁹⁰Yttrium brachytherapy, craniopharyngioma recurrence, vasopressin treatment, panhypopituitarism, treatment for psychiatric illness and follow-up duration. A prolonged follow-up duration significantly decreased the risk for increased fasting glucose (OR: 0.93, 95% CI: 0.88–0.97; $P<0.05$). Intracellar tumor location significantly protected for elevated triglycerides (OR: 0.43, 95% CI: 0.21–0.88; $P<0.05$) after adjustment for age and follow-up duration. Female sex (OR: 3.29, 95% CI: 1.35–8.01; $P<0.05$), ⁹⁰Yttrium brachytherapy (OR: 7.87, 95% CI: 1.58–39.2; $P<0.05$) and glucocorticoid replacement therapy (OR: 4.80, 95% CI: 1.12–20.6; $P<0.05$) were identified as significant risk factors for reduced HDL cholesterol after adjustment for hydrocephalus, craniopharyngioma recurrence and follow-up duration. Age (OR: 1.06, 95% CI: 1.02–1.10; $P<0.05$) significantly predicted elevated blood pressure after adjustment for

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Table 4 The MetS, its components, type 2 diabetes mellitus, and cardio- and cerebro-vascular morbidity in subgroups.

	♀ vs ♂	P value	CO vs AO	P value	GHRT vs non-GHRT	P value
MetS and its components						
MetS	54% vs 40%	0.09	48% vs 45%	0.71	43% vs 57%	0.24
Obesity	56% vs 48%	0.35	59% vs 45%	0.08	57% vs 43%	0.19
Increased fasting glucose	32% vs 41%	0.26	33% vs 39%	0.44	33% vs 40%	0.49
Elevated triglycerides	59% vs 49%	0.20	47% vs 60%	0.12	51% vs 58%	0.51
Reduced HDL cholesterol	58% vs 35%	<0.05	51% vs 42%	0.28	47% vs 38%	0.47
Elevated blood pressure	64% vs 47%	<0.05	46% vs 64%	<0.05	52% vs 67%	0.16
Type 2 diabetes mellitus and cardio- and cerebro-vascular morbidity						
Type 2 diabetes mellitus	14% vs 13%	0.70	11% vs 16%	0.34	10% vs 23%	0.08
HbA1c (mmol/mol) ^{a,b}	35 vs 34	0.74	33 vs 36	0.15	34 vs 37	0.72
Myocardial infarction	4% vs 2%	0.68	1% vs 5%	0.22	2% vs 7%	0.19
Cerebrovascular accident	9% vs 8%	0.82	7% vs 10%	0.59	6% vs 16%	0.13

^aMedian (range). ^bData available in 118 patients.

♀, female; ♂, male; AO, adult-onset craniopharyngioma; CO, childhood-onset craniopharyngioma; GHRT, treated growth hormone deficiency; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; MetS, metabolic syndrome; non-GHRT, untreated growth hormone deficiency.

female sex, childhood-onset craniopharyngioma and follow-up duration.

Since visual impairment was identified as a borderline significant predictor for the MetS (i.e. our primary study outcome), we compared baseline, tumor and treatment characteristics, as well as long-term health outcome between patients with and without visual impairment (Table 6). Craniopharyngioma treatment with ⁹⁰Yttrium brachytherapy (21% vs 6%; $P<0.05$) and tumor recurrence (47% vs 17%; $P<0.05$) were significantly more frequent in patients with

visual impairment compared to those with no visual impairment.

Type 2 diabetes mellitus and cardio- and cerebro-vascular morbidity

In our study, 24 (14%) patients suffered from type 2 diabetes mellitus (Table 3) and 11 of them received insulin treatment. In the subset of patients who were compared with the general population, prevalence of type 2 diabetes mellitus was significantly higher in patients

Table 5 Risk factors for the MetS in patients with craniopharyngioma.

Parameters	Univariable analysis		Multivariable analysis ^{c,d}	
	Odds ratio (95% CI)	P value	Odds ratio (95% CI)	P value
Age (in years)	1.01 (0.99–1.03)	0.22		
Female sex	1.69 (0.89–3.23)	0.11		
Childhood-onset disease	1.10 (0.58–2.09)	0.78		
Tumor location ^a				
Suprasellar	1.15 (0.15–8.71)	0.89		
Intra-/suprasellar	0.70 (0.09–5.20)	0.72		
Hydrocephalus	1.43 (0.69–2.98)	0.34		
Radiological hypothalamic damage	1.49 (0.76–2.94)	0.25		
Radiotherapy	1.29 (0.68–2.46)	0.43		
⁹⁰ Yttrium brachytherapy	2.61 (0.99–6.89)	0.05		
Craniopharyngioma recurrence	1.44 (0.74–2.77)	0.28		
Panhypopituitarism	1.43 (0.75–2.73)	0.28		
Treatment of GHD	0.58 (0.24–1.45)	0.24		
Sex steroid replacement ^b	2.57 (0.26–25.5)	0.42		
Glucocorticoid replacement	3.27 (1.22–8.74)	<0.05	2.32 (0.80–6.73)	0.12
Thyroid hormone replacement	2.72 (0.53–13.9)	0.23		
Vasopressin treatment	1.27 (0.65–2.48)	0.49		
Visual impairment	2.63 (1.11–6.24)	<0.05	2.54 (0.95–6.81)	0.06
Treatment for epilepsy	0.82 (0.25–2.69)	0.74		
Treatment for psychiatric illness	0.46 (0.18–1.19)	0.11		

^aCompared with intrasellar. ^bIn males and premenopausal females only. ^cAnalysis adjusted for follow-up duration. ^dCox and Snell $R^2=0.06$; model $\chi^2=6.87$; $P=0.08$.

CI, confidence interval; GHD, growth hormone deficiency; MetS, metabolic syndrome.

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Table 6 Comparison of patients with and without visual impairment.

	Visual impairment (n = 126)	No visual impairment (n = 35)	P value
Baseline characteristics			
♀ (n (%))	63 (50)	19 (54)	0.65
♂ (n (%))	63 (50)	16 (46)	
Age at diagnosis (years) ^a	26 (0–79)	17 (5–61)	0.26
Childhood-onset (n (%))	59 (47)	16 (46)	0.91
Adult-onset (n (%))	67 (53)	19 (54)	
Follow-up since diagnosis (years) ^a	16 (3–62)	17 (6–39)	0.49
Age at last follow-up assessment (years) ^a	48 (18–92)	47 (18–81)	0.71
Tumor characteristics			
Location (n (%))			0.88
Intrasellar	3 (3)	1 (3)	1.00
Suprasellar	49 (41)	12 (36)	0.62
Intra-/suprasellar	67 (56)	20 (61)	0.66
Hydrocephalus (n (%))	38 (30)	6 (18)	0.14
Radiological hypothalamic damage (n (%))	46 (39)	13 (41)	0.84
Craniopharyngioma treatment			
Neurosurgery (n (%))	120 (95)	31 (87)	0.23
Radiotherapy (n (%))	64 (51)	14 (40)	0.26
⁹⁰ Yttrium brachytherapy (n (%))	27 (21)	1 (6)	<0.05
Recurrence (n (%))	59 (47)	6 (17)	<0.05
Long-term health outcome			
Pituitary hormone deficiencies (n (%))			
GH	107 (87)	28 (80)	0.30
FSH/LH	109 (87)	30 (86)	0.78
ACTH	105 (83)	26 (74)	0.22
TSH	117 (94)	30 (86)	0.16
ADH	82 (65)	22 (63)	0.81
Panhypopituitarism	68 (54)	19 (54)	0.99
Body mass index (kg/m ²) ^a	30.4 (16.9–59.5)	31.0 (24.6–48.7)	0.47
Treatment for epilepsy (n (%))	12 (10)	1 (3)	0.30
Treatment for psychiatric illness (n (%))	15 (12)	6 (17)	0.41
MetS and its components			
MetS (n (%))	56 (52)	9 (29)	<0.05
Obesity (n (%))	60 (53)	19 (54)	0.86
Increased fasting glucose (n (%))	47 (41)	8 (26)	0.12
Elevated triglycerides (n (%))	60 (56)	13 (45)	0.30
Reduced HDL cholesterol (n (%))	52 (51)	10 (35)	0.13
Elevated blood pressure (n (%))	69 (56)	20 (57)	0.91

^aMedian (range).

♀, female; ♂, male; ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; FSH/LH, follicle stimulating hormone/luteinizing hormone; GH, growth hormone; GHD, growth hormone deficiency; GHRT, growth hormone replacement therapy; HDL, high-density lipoprotein; kg/m², kilograms per square meter; MetS, metabolic syndrome; n, number; TSH, thyroid-stimulating hormone.

with craniopharyngioma (11% vs 6% ($P < 0.05$) for Dutch patients; 17% vs 6% ($P < 0.05$) for Swedish patients). In our study, 6 (3%) patients with craniopharyngioma experienced a myocardial infarction, and 15 (8%) patients suffered from a cerebrovascular accident. One patient with childhood-onset craniopharyngioma had a myocardial infarction at the age of 38 years. In patients with adult-onset craniopharyngioma, the median age at myocardial infarction was 53 years (range: 32–73 years). Cerebrovascular accidents affected six patients with childhood-onset craniopharyngioma at a median age of 31 years (range: 19–38). The median age of cerebrovascular accident in patients with adult-onset craniopharyngioma

was 64 years (range: 35–77). Prevalence of type 2 diabetes mellitus, myocardial infarction and cerebrovascular accident, as well as HbA1c levels were similar in Dutch and Swedish patients with craniopharyngioma (Table 3), as well as in females and males, patients with childhood-onset and adult-onset craniopharyngioma, and patients with treated and untreated GHD (Table 4).

Discussion

We performed the largest study that investigated the MetS and its components in patients with craniopharyngioma to

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date. After a median follow-up duration of 16 years, almost half of the patients with craniopharyngioma demonstrated the MetS. Accordingly, in a subset of Dutch and Swedish patients who were compared with the general population, we found that the MetS was significantly more prevalent than expected. Using multivariable logistic regression analyses adjusted for follow-up duration, we identified visual impairment, radiological hypothalamic damage, tumor location, female sex, ^{90}Y trium brachytherapy, glucocorticoid replacement therapy and age as significant risk factors for the MetS and its components.

In our study, prevalence of the MetS in patients with craniopharyngioma was 46%. Other studies that investigated the MetS in patients with craniopharyngioma observed a prevalence between 8 and 67% (Table 7) (15, 16, 17, 18, 19, 20). This wide variation in prevalence may be related to heterogeneity in study populations and difference in definitions used to classify patients as exhibiting the MetS. In the subset of Dutch and Swedish patients with craniopharyngioma who were compared with the general population, we observed a significantly higher prevalence of the MetS than expected. This is in concordance with three small other studies that also compared the prevalence of the MetS between patients with craniopharyngioma and control subjects (15, 17, 18). Studies that investigated the MetS in patients with hypopituitarism due to various causes (including craniopharyngioma) did not observe any significant difference in the prevalence of the MetS between patients with craniopharyngioma and patients with hypopituitarism due to other causes, at least in patients with untreated GHD (18, 23, 24). Profka *et al.* observed that the beneficial metabolic effects of GHRT were less pronounced in patients with craniopharyngioma compared with patients with hypopituitarism due to non-functioning pituitary adenoma. In their study, prevalence of the MetS was significantly higher in patients with craniopharyngioma compared with patients with non-functioning pituitary adenoma after 5 years of GHRT (37% vs 5%; $P < 0.05$) (18).

The increased susceptibility for the MetS and its components in patients with craniopharyngioma is likely to be multifactorial. Tumor- and treatment-related damage of important brain structures, as well as their associated morbidities with currently available management options may altogether adversely affect metabolic function. This makes it challenging to evaluate risk factors for the MetS and its components. Nevertheless, we assessed patients with craniopharyngioma for predictors of an adverse metabolic state. Using multivariable logistic regression analyses adjusted for follow-up duration, we identified

visual impairment as a borderline significant risk factor for the MetS. Radiological hypothalamic damage significantly increased the risk for obesity. A prolonged follow-up duration significantly decreased the risk for increased fasting glucose. Intracellular tumor location significantly protected for elevated triglycerides. Female sex, ^{90}Y trium brachytherapy and glucocorticoid replacement therapy were identified as significant risk factors for reduced HDL cholesterol. Age significantly predicted elevated blood pressure. The increased risk for the MetS associated with visual impairment may be due to a negative effect of visual impairment on the ability to participate in physical activity. This is illustrated by studies that observed a significantly lower level of physical activity in patients with craniopharyngioma compared with age-matched, sex-matched and body mass index-matched control subjects (25, 26). A lower level of physical activity has been associated with an increased risk for the MetS in the general population (27). Differences in tumor characteristics between patients with and without visual impairment may also contribute to the increased risk for the MetS in patients with visual impairment. We found a significantly higher rate of craniopharyngioma recurrence and subsequent treatment with ^{90}Y trium brachytherapy in patients with visual impairment compared to those without visual impairment. Craniopharyngioma recurrence and additional treatment may exacerbate tumor- and treatment-related brain damage, thereby increasing the risk for the MetS and its components.

The increased risk for obesity associated with radiological hypothalamic damage may be due to acquired leptin and insulin resistance, as well as autonomic nervous system dysfunction. These factors may adversely affect food intake and energy expenditure, thereby promoting obesity (28). An increased risk for obesity in patients with craniopharyngioma associated with hypothalamic damage has also been observed in other studies (29, 30, 31, 32). We observed an increased risk for reduced HDL cholesterol associated with female sex. This may be due to currently used estrogen-progestin replacement regimens that do not fully simulate the physiological menstrual cycle (33). This is illustrated by a recent study that observed an improved cardiovascular risk profile in premature ovarian insufficient females treated with a more physiological transdermal/transvaginal estrogen-progestin replacement regimen compared with a regular oral estrogen-progestin replacement regimen (34). In our study, all premenopausal females with hypogonadotropic hypogonadism used a regular oral estrogen-progestin replacement regimen. The increased risk for reduced HDL

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Table 7 Studies investigating the MetS in patients with craniopharyngioma.

References	n	Median age at craniopharyngioma dx (range) (year)	Median age (range) (year)	Median follow-up (range) (year)	Pituitary hormone deficiencies	Definition MetS	Prevalence MetS ^a	Subgroup results
Pereira <i>et al.</i> (16)	♀ 30 ♂ 25	29 (4–74)	49 (6–76)	10 (1–37)	GH 89% ^b FSH/LH 88% ^c ACTH 88% TSH 84% ADH 53% Panhyp 89% GH 86% ^d FSH/LH 88% ^e ACTH 86% TSH 93% ADH 83% Panhyp 76% GH 53% ^g	NCEP	47%	♀ vs ♂ 57% vs 24% (<i>P</i> < 0.05)
Holmer <i>et al.</i> (15)	♀ 20 ♂ 22	12 (3–22)	28 (17–57)	20 (4–40)	GH 89% FSH/LH 88% ^c ACTH 88% TSH 84% ADH 53% Panhyp 89% GH 86% ^d FSH/LH 88% ^e ACTH 86% TSH 93% ADH 83% Panhyp 76% GH 53% ^g	IDF	26% vs 7% (<i>P</i> < 0.05)	TGTV vs non-TGTV 40% vs 6% (<i>P</i> < 0.05)
Simoneau-Roy <i>et al.</i> (17)	♀ 8 ♂ 7	NA	15 ± 4 ^f	5 ± 3 ^f	FSH/LH 33% ^h ACTH 93% TSH 93% ADH 93% Panhyp NA GH 100% ⁱ	Modified NCEP and WHO criteria	67% vs 20% (<i>P</i> < 0.05)	NA
Sahakitrungruang <i>et al.</i> (19)	♀ 5 ♂ 7	NA	14 (8–18)	2 (1–11)	FSH/LH 33% ^e ACTH 83% TSH NA ADH NA Panhyp NA GH 100% ^j FSH/LH 74% ^e ACTH 90% TSH 95% ADH 79% Panhyp 63% GH 96% ⁿ FSH/LH 96% ^e ACTH 88% TSH 96% ADH 63% Panhyp NA GH 85% ^p	Modified NCEP and WHO criteria	42% vs 8% (<i>P</i> = 0.16)	NA
Profka <i>et al.</i> (18)	♀ 7 ♂ 12	42 ± 13 ^f	47 ± 13 ^f	5 ± 0 ^f	FSH/LH 74% ^e ACTH 90% TSH 95% ADH 79% Panhyp 63% GH 96% ⁿ FSH/LH 96% ^e ACTH 88% TSH 96% ADH 63% Panhyp NA GH 85% ^p	NCEP	37% vs 5% (<i>P</i> < 0.05) ^k	GHRT vs non-GHRT 37% vs 31% ^l
Ferraù <i>et al.</i> (20)	♀ 12 ♂ 12	CO 15 ^m AO 9	38 ± 15 ^f	16 ± 9 ^f	FSH/LH 88% ^q ACTH 82% TSH 92% ADH 62% Panhyp 53%	IDF	8%	NA
Wijnen <i>et al.</i> ^o (3)	♀ 90 ♂ 88	23 (0–79)	47 (18–92)	16 (3–62)	FSH/LH 88% ^q ACTH 82% TSH 92% ADH 62% Panhyp 53%	Joint interim statement	Dutch 46% vs 29% (<i>P</i> < 0.05) ^r Swedish 52% vs 15% (<i>P</i> < 0.05) ^s	♀ vs ♂ 54% vs 40% (<i>P</i> = 0.09) CO vs AO 48% vs 45% (<i>P</i> = 0.71) GHRT vs non-GHRT 43% vs 57% (<i>P</i> = 0.24)

^aCompared with control subjects. ^bMajority of patients with GHD received no GHRT (exact number of patients not mentioned). ^cNumber of patients receiving sex steroid replacement therapy not mentioned. ^d95% of patients with GHD received GHRT. ^eAll patients with hypogonadotropic hypogonadism received sex steroid replacement therapy. ^fMean ± s.d. ^gGHD not formally tested; only (pre)pubertal patients with growth failure received GHRT. ^hNot mentioned how many patients exhibited hypogonadotropic hypogonadism; 33% of all patients received sex steroid replacement therapy. ⁱNo patients with GHD received GHRT. ^jAll patients with GHD received GHRT. ^kCompared with patients with non-functioning pituitary adenoma. ^lPrevalence of the MetS after five years of GHRT compared with baseline before the start of GHRT. ^mChildhood-onset defined as ≤18 years at craniopharyngioma diagnosis. ⁿ70% of patients with GHD received GHRT. ^oPresent study. ^p79% of patients with GHD received GHRT. ^q95% of patients with hypogonadotropic hypogonadism received sex steroid replacement therapy. ^rSubset of Dutch patients with craniopharyngioma aged 30–70 years compared with the general population. ^sSubset of Swedish patients with craniopharyngioma aged 45–69 years compared with the general population. ♀, female; ♂, male; ACTH, adrenocorticotrophic hormone; ADH, antidiuretic hormone; AO, adult-onset craniopharyngioma; CO, childhood-onset craniopharyngioma; dx, diagnosis; FSH/LH, follicle stimulating hormone/luteinizing hormone; GH, growth hormone; GHD, growth hormone deficiency; GHRT, growth hormone replacement therapy; IDF, International Diabetes Federation; MetS, metabolic syndrome; n, number; NA, not available; NCEP, National Cholesterol Education Program; Panhyp, panhypopituitarism; TGTV, tumor growth into third ventricle; TSH, thyroid stimulating hormone; WHO, World Health Organization.

cholesterol associated with glucocorticoid replacement therapy may be due to currently available glucocorticoid replacement regimens that contain relatively high glucocorticoid doses and are administered in patterns that do not fully simulate the physiological circadian cortisol rhythm in terms of serum level and pulsatility (35).

Some limitations of our study should be considered. Data on waist circumference were unavailable. This may have led to an underestimation of the prevalence of the MetS and obesity, because those patients with an elevated waist circumference but body mass index $\leq 30 \text{ kg/m}^2$ were misclassified as non-obese. However, we anticipate that this misclassification is small, since several studies advocated that a body mass index of $>30 \text{ kg/m}^2$ may be used to diagnose obesity as a component of the MetS instead of elevated waist circumference (14, 36, 37). Moreover, a recent study by Gierach *et al.* reported a high and significant correlation between body mass index and waist circumference in patients with the MetS ($R=0.78$; $P<0.01$) (38). The 'NL de Maat' study and 'LSH' study, which were used for the comparisons with the general population, classified participants as obese by waist circumference (21, 22). Otherwise, there were no substantial differences in the criteria used to define the MetS and its components between our study and the 'NL de Maat' study and 'LSH' study. Unfortunately, both the 'NL de Maat' study and 'LSH' study did not report data on increased fasting glucose. Therefore, we were unable to study the prevalence of increased fasting glucose in patients with craniopharyngioma relative to the general population. Another limitation of our study is that we were unable to investigate the prevalence of the MetS relative to the general population after adjustment for obesity. Interestingly, when analyzing our data, the prevalence of the MetS seems to be lower than the prevalence of obesity in patients with craniopharyngioma, while in the Dutch general population the prevalence of the MetS seems to be higher than the prevalence of obesity. Since visceral adipose tissue-induced insulin resistance is postulated to be the principal factor resulting in the MetS and its components (7), this indicates that one may expect an even higher prevalence of the MetS in patients with craniopharyngioma. Future studies should clarify this issue. Other limitations of our study include the unavailability of data on ethnicity, lifestyle factors, histological subtype of craniopharyngioma (i.e. adamantinomatous or papillary) and body composition measured by dual-energy X-ray absorptiometry (DXA). Body composition measured by DXA has been shown to be a better predictor for cardiovascular and cerebrovascular morbidity than body composition measured by anthropometry (39, 40).

In conclusion, we observed a high prevalence of the MetS and its components in patients with craniopharyngioma. In a subset of Dutch and Swedish patients with craniopharyngioma who were compared with the general population, we found that the MetS was significantly more prevalent than expected. Using multivariable logistic regression analyses adjusted for follow-up duration, we identified visual impairment, radiological hypothalamic damage, tumor location, female sex, $^{90}\text{Yttrium}$ brachytherapy, glucocorticoid replacement therapy and age as significant risk factors for the MetS and its components in patients with craniopharyngioma.

Supplementary data

This is linked to the online version of the paper at <https://doi.org/10.1530/EJE-17-0387>.

Declaration of interest

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

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