CLINICAL STUDY

Quality of life in treated adult craniopharyngioma patients

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Abstract

Objective: Quality of life (QoL) has become increasingly important in the evaluation of treatment of pituitary and hormonal diseases. A reduced QoL has been reported in childhood-onset craniopharyngioma; however, reports of QoL in adult craniopharyngioma patients are scarce. In the present study, we assessed QoL in adult patients successfully treated for craniopharyngioma in our centre.

Design: This was a case-control study.

Methods: In this study, we assessed QoL in 29 adult patients in remission during long-term follow-up after treatment for craniopharyngioma. Four validated health-related questionnaires (HADS, MFI-20, NHP and SF-36) were used, covering multiple aspects of physical, psychological and social functioning. Patient outcomes were compared to controls ($n = 142$) and to age-adjusted reference values derived from literature.

Results: General fatigue, physical fatigue, energy, physical condition and physical mobility were significantly impaired, compared with controls. The main independent predictors for decreased QoL were visual field defects (depression, total HADS score, activity, motivation and energy), female gender (depression, motivation and pain), repeat surgery (role limitations due to emotional problems) and radiotherapy (mental fatigue) (the last two predictors to a lesser extent).

Conclusion: Adult patients treated for craniopharyngioma show persistent impairment in QoL, especially in the physical subscales.

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Introduction

Craniopharyngiomas are histologically benign brain tumours arising from the remnants of Rathke's pouch. Despite their benign appearance, their clinical behaviour is aggressive, causing serious morbidity by damaging the optic chiasm, the pituitary, and hypothalamic area. Currently, craniopharyngioma is treated primarily by trans-sphenoidal or transcranial surgery, whereas post-surgical radiotherapy is not routinely applied in all patients (1, 2). Recurrent disease is treated by repeat surgery and/or radiotherapy.

In adults, treatment of craniopharyngioma is associated with excessive multisystem morbidity and increased mortality during long-term follow-up despite a high cure rate (3–6). There is a high incidence of pituitary insufficiencies, and visual field defects may persist in some patients (1–4). Finally, there is a high incidence of cardiovascular risk factors in these patients (1, 3, 4).

Pituitary diseases in general are associated with decreased quality of life (QoL) and cognitive dysfunction, despite optimal replacement strategies for pituitary insufficiency, and long-term cure of hormone

excess syndromes such as Cushing's disease and acromegaly (7–10). Hypopituitarism and radiotherapy are important factors for impaired QoL. Reduced QoL has been reported in childhood-onset craniopharyngioma (3, 11–13). To our knowledge, QoL in adult craniopharyngioma patients has been reported in only one study (3). In this study, QoL was markedly reduced, as assessed by two questionnaires, NHP and QoL-AGHDA, the latter being a disease-specific questionnaire, designed to assess physical and psychological discomfort in adult growth hormone deficiency. Given the high prevalence of associated morbidity found in our adult craniopharyngioma patients (4), we wanted to extend these observations by assessment of QoL in more detail.

In the present study, we assessed QoL in adult patients successfully treated for craniopharyngioma in our centre. We evaluated physical, psychological, and social aspects of QoL in patients after long-term cure, using four validated, health-related QoL questionnaires. Patient outcomes were compared with our own control values as well as to age-adjusted reference values derived from literature.

Patients and methods

Protocol

We identified 43 patients treated and cured for craniopharyngioma, followed in our centre from 1965 to 2002. Four QoL questionnaires were sent to their homes. They were asked to participate, and to complete and return the questionnaires in a prepaid envelope. Non-responders received a reminder letter. Thereafter, they were contacted once by telephone and encouraged to complete and return the questionnaires. Patients were also asked to provide a control person with comparable age and sex (such as a relative – but not the partner – friend or neighbour) in order to compose a control population with similar socio-economic status derived from the same geographical area. In addition to this control group, we used literature reference data from healthy samples of the Dutch and west European population from studies reporting normal age-adjusted values (14–18). These data are based on larger study populations than our own controls and are therefore not affected by a potential positive selection by the patients.

The medical ethics committee of Leiden University Medical Center approved the study protocol.

Patients and controls (Table 1)

Thirty-three of 43 (77%) patients returned the questionnaires, four of whom preferred not to participate. Thus, 29 completed questionnaires were received. The study population of 29 patients (15 males) had a mean age of 47.9 ± 17.6 years (range 11–80 years). All patients were primarily treated by surgery. Nine patients received radiotherapy, four for recurrence. Seven patients had repeat surgery. Mean follow-up after primary surgery was 19.9 ± 13.1 years, and all patients were cured of disease. Hypopituitarism was present in 93% of cases. No significant differences in age, gender and tumour characteristics were found

between the study population and the patients who did not return the questionnaires.

Twenty-five controls returned completed questionnaires. The control group was extended by controls derived from other studies performed at our centre, who had been similarly approached (7, 9). Therefore, the total control group consisted of 142 controls (88 females, 54 males), with a mean age of 53.8 ± 14.5 years. No significant differences in QoL measures were present between the three control groups, justifying their combined use. Age and gender were not significantly different from the studied craniopharyngioma patients.

Study parameters

Primary study parameters were the results of four health-related QoL questionnaires. The results were linked to patient characteristics (age and sex), applied treatments (surgery, radiotherapy and multiple surgical procedures), presence of hypopituitarism and visual impairments. Hypopituitarism was defined as one or more pituitary hormone deficiencies.

Questionnaires

HADS (Hospital Anxiety and Depression Scale) The HADS consists of 14 items pertaining to anxiety and depression. Each item is measured on a 4-point scale. The range of scores for the anxiety and depression subscale is 0–21; for the total score, 0–42. A high score points to more severe anxiety and depression (19). Age-related Dutch reference values of the general population were derived from the study of Spinhoven *et al.* (16).

MFI-20 (Multidimensional Fatigue Index) The MFI-20 contains 20 statements to assess fatigue (20). The following five different dimensions of fatigue (four items each) are calculated from these statements:

Table 1 Characteristics of the craniopharyngioma patients and controls.

	Craniopharyngioma patients (<i>n</i> = 29)	Controls (<i>n</i> = 142)
Age (years)	47.9 ± 17.6	53.8 ± 14.5 (<i>P</i> = NS)
Male/female	15/14	88/54 (<i>P</i> = NS)
Age at diagnosis (years)	27.9 ± 16.2	
Childhood onset	8 (28%)	
Radiotherapy	9 (31%)	
Repeat surgery	7 (24%)	
Persistent visual field defects	12 (41%)	
Intact pituitary function	2 (7%)	
Single pituitary deficiency	0	
Multiple pituitary deficiencies*	5 (17%)	
Panhypopituitarism**	22 (76%)	

NS: not significant.

* Defined as pituitary deficiency in more than one axis.

** Defined as pituitary deficiency in all four axes.

1. general fatigue
2. physical fatigue
3. reduced activity
4. reduced motivation
5. mental fatigue.

Every statement is measured on a 5-point scale; scores range from 0 to 20. Higher scores indicate higher experienced fatigue. Age-related Dutch reference values were derived from Smets *et al.* (15).

NHP (Nottingham Health Profile) The NHP is frequently used in patients with pituitary disease to assess general well-being and QoL. The survey consists of 38 yes/no questions, subdivided into the following six scales assessing impairments:

1. pain (eight items)
2. energy level (three items)
3. sleep (five items)
4. emotional reactions (nine items)
5. social isolation (five items)
6. disability/functioning, that is, physical ability (eight items) (21, 22).

Subscale scores are calculated as a weighted mean of the associated items and are expressed as a value between 0 and 100. The total score is the mean of the six subscales. Higher scores are related to worse QoL. Age-related, west European reference values were derived from the study by Hinz *et al.* (14).

SF-36 (Short Form-36) The SF-36 questionnaire comprises 36 items and records general well-being during the previous 30 days (23, 24). The items are formulated as statements or questions to assess the following eight health concepts:

1. physical functioning
2. social functioning
3. limitations in usual role activities because of physical health problems
4. pain
5. general mental health (psychological distress and well-being)
6. limitations in usual role activities because of emotional problems
7. vitality (energy and fatigue)
8. general health perceptions and change in health.

Because the HADS and the MFI-20 are more specific questionnaires for mental health and fatigue, the vitality and general mental health items were left out in this evaluation. Scores are expressed on a 0–100 scale. Higher scores are associated with better QoL. Age-related, west European reference values were derived from van der Zee *et al.* (17, 18).

Statistics

SPSS for Windows, Version 12.0 (SPSS Inc., Chicago, IL, USA), was used to perform data analysis. Data are expressed as mean $\pm$ s.d. unless otherwise mentioned. We used unpaired *t*-tests to compare patient and control data. Using linear regression analysis, we assessed independent variables that affect quality of life. Differences were considered statistically significant at $P = 0.05$ or less.

Results

Patient characteristics (Table 1 and Fig. 1)

Clinical characteristics are detailed in Table 1. Primary surgery was performed in all 29 patients. Nine (31%) patients received radiotherapy after primary surgery, and seven patients (24%) needed more than one operation. The different treatment modalities are summarized in Fig. 1. At the time of evaluation, pituitary function in two patients was intact. These two patients were both reoperated because of tumour regrowth, and both suffered from visual field defects. Five (17%) patients had pituitary deficiency in three of four axes. In the majority of patients (76%), panhypopituitarism was present. Twelve (41%) patients had persistent visual impairment.

QoL in craniopharyngioma patients and controls (Table 2)

Compared with the 142 controls and the age-adjusted reference values, the craniopharyngioma patients had reduced QoL in every questionnaire, except for HADS. According to HADS, there was no significant difference between patients and controls in items concerning anxiety and depression. All subscales of fatigue assessed by the MFI-20 were affected, especially general and

Figure 1 Patient groups, stratified by different treatment modalities. RT: radiotherapy.

Table 2 Quality of life (HADS, MFI-20, NHP and SF-36) in treated craniopharyngioma patients compared to controls and age-adjusted reference values.

	Craniopharyngioma patients (n = 29)	Controls (n = 142)	P value ^a	Age-adjusted reference values ^b	P value ^c
HADS					
Anxiety	3.59±3.15	4.02±3.21	NS	4.89±3.60	NS
Depression	3.31±3.01	3.33±3.02	NS	3.61±3.35	NS
Total	6.90±5.41	7.35±5.43	NS	8.42±6.32	NS
MFI-20					
General fatigue	11.76±4.20	8.33±3.76	<0.001	9.91±5.20	<0.025
Physical fatigue	11.57±4.33	7.87±3.89	<0.001	8.79±4.90	<0.005
Reduction in activity	9.69±4.10	7.39±3.45	<0.01	8.69±4.60	NS
Reduction in motivation	9.61±4.11	7.73±3.83	<0.05	8.23±4.00	NS
Mental fatigue	9.62±4.66	8.00±4.10	<0.1	8.33±4.80	NS
NHP					
Energy	20.11±28.63	5.55±18.01	<0.001	10.34±25.5	<0.05
Pain	9.42±19.91	5.54±14.38	NS	6.17±18.4	NS
Emotional reaction	9.11±18.56	5.47±15.33	NS	7.31±16.2	NS
Sleep	12.08±16.65	9.18±22.21	NS	12.86±25	NS
Physical ability	11.43±19.15	5.68±12.97	<0.05	4.69±13.9	0.05
Social isolation	6.57±18.77	1.67±7.74	<0.05	5.38±16	NS
NHP total score	11.41±13.73	5.31±10.42	<0.01	d	
SF-36					
Physical functioning	72.24±24.30	85.92±19.42	<0.001	79.16±21.59	NS
Social functioning	83.62±19.79	90.96±17.04	<0.05	86.28±20.77	NS
Role limitations due to physical problems	79.46±28.91	87.86±27.56	NS	77.66±36.24	NS
Role limitations due to emotional problems	94.05±20.39	88.57±28.21	NS	83.73±32.31	NS
Pain	80.51±16.88	85.83±19.14	NS	79.70±25.05	NS
General health perception	54.82±26.19	72.02±17.79	<0.01	69.43±21.89	<0.005
Health change	50.86±21.63	56.91±18.69	NS	51.44±18.54	NS

Data shown are the mean±s.d.

^a Patients compared with own controls by the unpaired, two-tailed *t*-test.^b Derived from references 14–18.^c Patients compared with literature reference data by the unpaired, two-tailed *t*-test.^d No data available.

physical fatigue. Reduction in activity and motivation did not reach statistical significance when compared with the age-adjusted reference values. The scores of the patients on the NHP pointed to reduced energy and physical mobility. Sleep, emotional reaction and social isolation scores were not significantly different from the controls. Health perception, as assessed by the SF-36, was significantly affected in craniopharyngioma patients. Moreover, physical and social functioning was reduced, as compared with own controls.

Factors affecting QoL in craniopharyngioma patients

Childhood- versus adult-onset craniopharyngioma

Adult-onset craniopharyngioma patients performed worse on the depression score (HADS, $P < 0.05$) than childhood-onset patients.

Gender Compared with males, females reported decreased QoL for several energy-related items, such as general fatigue (MFI-20, $P < 0.01$), reduced motivation (MFI-20, $P < 0.05$) and energy (NHP, $P < 0.01$), and

also for pain (NHP, $P < 0.05$), social functioning (SF-36, $P < 0.05$) and role limitations due to physical problems (SF-36, $P < 0.05$).

Age Younger patients were more affected on the following subscales: social isolation (NHP, $P < 0.05$) and social functioning (SF-36, $P < 0.05$). No age-related differences were found on items concerning energy and physical functioning.

Radiotherapy Only mental fatigue was significantly affected in patients treated by radiotherapy (MFI-20, $P < 0.01$).

Repeat surgery Patients who underwent multiple operations performed worse on general fatigue (MFI-20, $P < 0.05$), sleep (NHP, $P < 0.05$) and health change (SF-36, $P < 0.01$).

Visual field defects The presence of persistent visual field defects significantly affected the following items: total HADS score ($P < 0.05$), general fatigue (MFI-20, $P < 0.05$), reduced activity (MFI-20, $P < 0.01$), reduced motivation (MFI-20, $P < 0.01$), energy

(NHP, $P < 0.01$), social functioning (SF-36, $P < 0.05$) and role limitations due to physical problems (SF-36, $P < 0.05$).

Multiple pituitary deficiencies/panhypopituitarism

Scores from patients with intact pituitary function ($n = 2$) indicated more reduced QoL in all subscales of the HADS and the MFI-20, as compared with patients with multiple pituitary deficiencies/panhypopituitarism. However, the SF-36 scores from patients with multiple pituitary deficiencies/panhypopituitarism were lower, indicating more reduced QoL; according to the NHP, no obvious differences in scores were observed.

Linear regression Stepwise, univariate, linear regression analysis was performed in a model including gender, age, radiotherapy, multiple pituitary deficiencies/panhypopituitarism, multiple operations and visual defects as independent variables, and the questionnaire items as dependent variable. Visual field defect was an independent predictor for depression (HADS, $P = 0.05$), total HADS score ($P < 0.05$), reduced activity (MFI-20, $P = 0.05$), reduced motivation (MFI-20, $P < 0.01$) and reduced energy (NHP, $P < 0.05$). Female gender was an independent predictor for depression (HADS, $P < 0.05$), reduced motivation (MFI-20, $P < 0.05$) and pain (NHP, $P = 0.05$). Radiotherapy was an independent predictor for mental fatigue (MFI-20, $P < 0.05$). Repeat surgery correlated to role limitations due to emotional problems (SF-36, $P < 0.05$). Multiple pituitary deficiencies/panhypopituitarism was not an independent predictor for any of the questionnaire items.

Discussion

Despite long-term cure, adult craniopharyngioma patients experience a considerable decrease in QoL. The decrease in QoL was mainly manifested in the physical items and, to a lesser extent, in psychosocial items. QoL in adult craniopharyngioma patients is mostly affected by visual impairment and less by female gender, repeat surgery and radiotherapy.

The survival prognosis of patients treated for craniopharyngioma is favourable, with reported 10-year survival rates of approximately 90% in both adults and children (1, 11, 25–27), although a lower survival rate has been reported (6). Clinical symptoms may arise from both tumour mass effects and effects of treatment. In addition to the well-recognized signs and symptoms secondary to hormonal deficiencies and visual deficits, patients experience physical and neuropsychological deficits, such as obesity, and deficits of higher cortical function, memory, and behaviour (1, 11, 13). Decreased QoL in children treated for craniopharyngioma has been reported, affecting both physical and psychosocial health (2, 3, 11–13). To date, structured QoL research in adult patients

treated for craniopharyngioma has been studied in only one report (3). In this study, according to the NHP and the QoL-AGHDA questionnaires, QoL was markedly reduced. Our series reports a broader assessment of QoL, which also focuses on fatigue and energy (MFI-20), as well as anxiety and depression (HADS). We applied four different questionnaires, covering multiple aspects of physical, psychological and social functioning.

In the present study, QoL in patients treated for craniopharyngioma proved to be more affected in items concerning physical performance than in psychosocial performance. General fatigue, physical fatigue, energy, physical condition and mobility were significantly affected, as compared with controls. This agrees with the high prevalence of metabolic and visual morbidity found in adult craniopharyngioma, which is attributed to irreversible hypothalamic, and optic damage (3, 4). Accordingly, the main independent predictors affecting QoL were found to be visual field defects and, to a lesser extent, multiple operations, female gender and radiotherapy. However, because of the relatively small number of patients, the results of the linear regression analysis have to be interpreted with caution. Multiple pituitary deficiencies or panhypopituitarism was found in all except two craniopharyngioma patients. Because of the small number of patients with intact pituitary function, the potential contribution of hypopituitarism to the reduced QoL could not be assessed statistically. Hypopituitarism was found to be an independent predictor of reduced QoL in patients treated for Cushing's disease and acromegaly, affecting both physical and psychosocial items (7, 9). Despite optimal substitution, it is likely that hypopituitarism in our patient group also contributes to reduced QoL. SF-36 scores from our craniopharyngioma patients, 93% of whom had pituitary deficiencies in at least three axes, were comparable to scores in patients with two or three pituitary deficiencies after treatment for non-functioning pituitary adenomas (8). However, our craniopharyngioma patients report better QoL scores in all four questionnaires than treated Cushing patients with hypopituitarism (9), pointing to a significant contribution of hypercortisolism to reduced QoL.

The predisposition to female gender as an independent risk factor for decreased QoL in craniopharyngioma is unclear, although it does not seem to be a disease-specific phenomenon. In the general population, female gender is also associated with higher scores on the NHP, indicating lower QoL (14). QoL studies in non-pituitary diseases (malignancies, coronary heart disease and inflammatory bowel disease) also report decreased QoL in female patients as compared with male patients (28–32).

Thirty-three of 43 (77%) patients returned the questionnaires, four of whom preferred not to participate because of physical invalidation. Participation of these

four patients, however, would even have worsened QoL scores, because they suffered from serious morbidity. The use of controls chosen by the patients may have introduced a bias, since controls with supposedly good QoL are more likely to be asked. To overcome this possible bias, we also used validated reference data from literature (14–18). Compared with those age-adjusted reference values, QoL parameters were affected significantly in fewer subscales than was revealed by the comparison with our own controls. This suggests that patients chose controls with a supposed good health status. Nonetheless, the comparison with both sources of control data revealed the same pattern; that is, adult craniopharyngioma patients had seriously impaired QoL.

In conclusion, QoL in adult craniopharyngioma patients is significantly reduced compared with a healthy population, especially in the physical items. The main independent predictor of a worse QoL is visual field defects. Despite long-term cure, treatment of craniopharyngioma to prevent recurrence does not normalize QoL.

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