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Pituitary tumors, transsphenoidal surgery and headache - a prospective cohort study

Degree Project in Medicine

Agnes Andersson

Program in Medicine

Gothenburg, Sweden 2019

Supervisor: Thomas Skoglund

Department of Neurosurgery, Sahlgrenska University hospital

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Abstract

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Agnes Andersson, 2019, Department of Neurosurgery, Sahlgrenska University Hostpital, Gothenburg, Sweden

Background

Headache is a common symptom in patients with pituitary tumors, yet insufficiently investigated with respect to mechanisms and treatment strategies. Headache is currently not an indication for surgical tumor resection.

Objectives

The objectives of the present study were to investigate the prevalence of headache in patients before and six months after endoscopic transsphenoidal surgery, and to study the correlations between headache and both patient and tumor characteristics.

Methods

Patients with pituitary tumors admitted to Sahlgrenska University Hospital for endoscopic surgery were prospectively enrolled in the study. Disability related to headache was quantified preoperatively and six months after surgery. Tumor characteristics were collected from medical records: tumor size </>1 cm, suprasellar growth, chiasm compression, invasion of cavernous sinus and tumor histology. Analyses were conducted in order to identify relationships between tumor/patient factors and both headache and headache response to surgery.

Results

Out of the 119 patients included in the study preoperatively, disability due to headache was present in 35%. Tumor size <1 cm was significantly associated to headache related disability ($p=0.016$), as well as female sex and young age ($p=0.018$, $p<0.001$). No significant correlations between disability due to headache and tumor histology, cavernous sinus invasion, chiasm compression or suprasellar extension were found. Headache data was collected six months postoperatively from 89 patients. 21 patients reported a lower MIDAS score postoperatively, ten patients out of these

experienced full resolution. 18 patients reported deterioration postoperatively. Looking at patients with baseline headache disability alone (n=31), a significantly reduced disability grade (p=0.003) could be noted. A reduction in headache related disability was found to be significantly associated to tumor size <1 cm (p=0.003).

Implications

These results do not support headache as a sole indication for surgery. Further research on pituitary microadenomas headache-causing mechanisms and possible resolution through surgery is motivated.

Key words

Pituitary tumor, headache, endoscopic, transsphenoidal, surgery

Abbreviations used in this thesis

PG = Pituitary Gland
PA = Pituitary Adenoma
NFPA = Non Functioning Pituitary Adenoma
TTH = Tension Type Headache
MIDAS = Migraine Disability Assessment
HIT-6 = Headache Impact Test
GoPT = Gothenburg Pituitary Tumor study
TSS = Transsphenoidal surgery
GH = Growth Hormone
TSH = Thyreoptropin Stimulating Hormone
LH = Luteineizing Hormone
FSH = Follicle-stimulating Hormone
ACTH = Adenocorticotroph Hormone
PRL = Prolactinoma

Introduction

Pituitary tumors: prevalence and diagnosis

Pituitary tumors are common intracranial neoplasms with an estimated prevalence of 17% globally. This estimation is based on results from postmortem- and radiography studies, with estimates ranging from 1%-40%[8]. The majority of pituitary tumors remain undetected during the patients' lifetime. The global prevalence of diagnosed pituitary tumors is estimated to 0.03-0.05%[35]. In Sweden, with just over 10 million inhabitants, approximately 400 pituitary adenomas (PAs) are diagnosed every year and represent 90% of the total occurrences of pituitary tumors[26]. The incidence rate is increasing as a result of more frequent use of MRI (Magnetic resonance imaging). Asymptomatic pituitary tumors are, therefore, being detected to a greater extent in patients examined with brain imaging for various non-pituitary-related reasons.

Symptoms of pituitary tumors are related to either hormone abnormalities or compression of adjacent structures, such as the optic chiasm, cavernous sinus and the hypothalamus. Typically, pituitary tumors grow slowly, and symptoms develop gradually. In few cases, acute neurological symptoms develop due to intratumoral bleeding (pituitary apoplexy), causing rapid intrasellar expansion[23].

The pituitary tumors can be either hormone producing or non-functioning. The most common types of pituitary tumors are non-functioning pituitary adenomas (NFPAs) (30%) and prolactinomas (30%), followed by growth hormone-producing adenomas (GH)(20%), adenocorticotropic hormone-producing adenomas (ACTH)(8%) and thyrotropin- and luteinizing/follicle stimulating hormone (TSH, LH, FSH)(1%). The remaining 10% consist of non-adenomas such as craniopharyngeomas, meningeomas, granulomas, metastatis, cysts etc.[26].

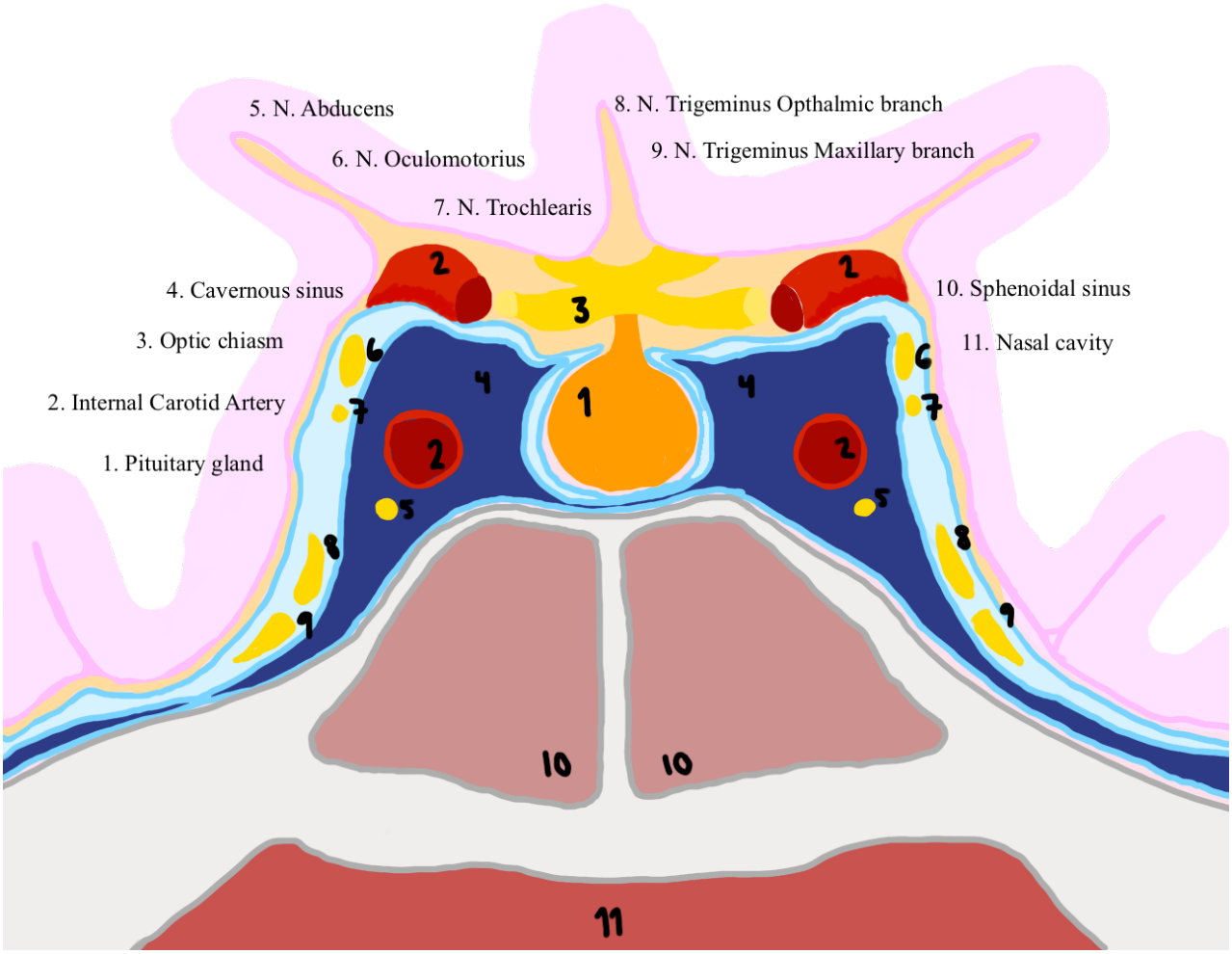

Fig. 1 Schematic view of the pituitary gland and its surroundings from a coronary section

Headache in patients with pituitary tumors

Headache is reported in up to 70% of patients with pituitary tumors[18]. The prevalence of headache is consistently higher in patients with growth hormone-producing tumors, prolactinomas and TSH-producing tumors[18,20]. The characteristics of headache in patients with pituitary tumors vary, the most common being migraine-like headaches and tension type headaches (TTH)[6]. The same is true for the total population[32]. While migraine-like headaches and TTH do not necessarily occur on account of a pituitary mass, the possibility cannot be discarded even in the presence of such a mass. If headache arises in the same time frame as the discovery of a pituitary tumor, it might indicate a relationship. Other rare types of headaches in these patients are SUNCT (short-lasting, unilateral, neuralgiform headache attacks with conjunctival injection and tearing), cluster headache, hemicrania continua and pain outside of the trigeminal territory[3,16,20].

Theories of headache-causing mechanisms from a pituitary tumor can roughly be divided into two categories; physical and biochemical mechanisms. The pituitary gland (PG) sits in a bony pit in the skull base called the sella turcica. Laterally, the sella is bordered by the cavernous sinuses through which several pain-sensitive structures run, such as the internal carotids and ophthalmic branches of the trigeminal nerves. Immediately above the PG, separated from it by the diaphragm sellae, lies the optic chiasm[21]. The PG and its anatomical surroundings are schematically described in **Fig. 1**. One theory of how a brain tumor can physically induce pain is by compressing nerves or innervated structures[34]. Originating from this, cavernous sinus invasion and tumor volume have been the main subjects for investigation regarding an eventual causal relationship with headache. Another physical theory is that headache is caused by increased intrasellar pressure[14]. The sella turcica, limited by the diaphragm sellae, constitutes its own separated intracranial space where the pressure could be affected by internal volume changes.

The biochemical mechanisms suggested as causes of headache are intratumoral expression of substances earlier found to be involved in pain transmission: substance P, Calcitonin gene related peptide and pituitary adenylate cyclase activating protein[17,37]. Dopamine agonist therapy in patients with prolactinomas has been observed to cause either headache relief or exacerbation[33]. This, and the observation that somatostatin analogs relieve headache in patients with acromegaly, indicates that there is a biochemical mechanism for headaches[19].

Clinical studies of patients with pituitary tumors have found significant correlations between headache and family history of headache, young age, female sex, nicotine use and highly proliferative tumors (Ki67-labelling index >3%) [18,28,29]. In most studies, tumor volume, invasion of cavernous sinus, biochemical/neuroendocrine mechanisms and chiasm compression have not been shown to be predictors of headaches[24,29,36]. Gondim et al. suggest in a 2009 study that macroadenomas, chiasm compression, cavernous sinus invasion and sellar destruction were all associated with headaches[12]. Wolf. et al. (2016) found the opposite relationship, e.g that microadenomas were more prone to headaches[36].

Most researchers familiar with this area agree that the reason for headache in patients with PA is multifactorial, including the patient's predisposition for headache as well as the physical and biochemical properties of the tumor. Size alone is not responsible for the occurrence of headaches. Multiple case reports exist, however, where the patients symptoms were trigeminal neuralgia ipsilateral to a cavernous sinus invasion and immediate postoperative relief occurred. This supports, of course, a pure physical tumor-mechanism causing headache[10,11].

Transsphenoidal tumor extirpation and impact on headaches

Treatments of patients with pituitary tumors require a multidisciplinar approach, with the involvement of neurosurgeons, endocrinologists, neuro-ophtalmologists, radiologists, oncologists and pathologists[26]. With the exception of prolactinomas, endoscopic surgery is the standard treatment for all symptomatic pituitary tumors. 90% of patients with prolactinomas reach normal serum prolactin levels through treatment with dopamine agonists. Other hormone secreting tumors are treated medically in cases where surgery is not an option due to comorbidities, or as a complement to surgery.

NFPAs are surgically removed if they grow to affect their surroundings, which usually involves compression of the optic chiasm and subsequent visual deterioration [26]. When this is not the case, watchful waiting with continuous MRIs and visual field examinations is applied[33]. Headache as symptom alone is not an indication for surgery in most patients with pituitary tumors[7].

A few studies exist that are investigating whether transsphenoidal surgery is an effective treatment for headaches in these patients. A prospective cohort study on 79 patients with pituitary adenomas showed a significant reduction of headache 6 months after transsphenoidal surgery (TSS). The same study looking exclusively at the NFPA-patients (n=60) showed that they also had significantly reduced headache scores, quantified with HIT-6 (Headache Impact Test, which closely resembles MIDAS* in purpose and configuration)[27]. A similar study found no significant headache reduction in their cohort (n=68)[29]. A study looking at microadenomas operated with TSS found

**Migraine Disability Assessment*

85% of patients experienced headache relief and resolution in 58%[9].

In conclusion, some research has been conducted in order to investigate the prevalence, character, mechanisms and treatment effects regarding headache in patients with pituitary tumors. The results are inconclusive and do not constitute a sufficient basis for treatment guidelines. Most researchers mention the necessity of larger scale prospective studies in order to shed light on what position headache should take in evaluating and treating patients with pituitary tumors.

Aim

The aim of this study is to analyze the prevalence of headache among patients scheduled for transsphenoidal resection of a pituitary tumor. Also, to see whether headache is more likely to be present in any specific patient category, depending on some tumor or patient characteristic. Finally, the aim is to find out if transsphenoidal resection relieves headache in these patients, or to identify a subgroup of patients where having headache as an indication for surgery might be appropriate.

Methods

The data was derived from the Gothenburg Pituitary Tumor study (GoPT), a prospective study that enrolls patients scheduled for pituitary surgery at Sahlgrenska University Hospital, sole provider of neurosurgical services for 1.8 million people in the western region of Sweden. Between September 2015 and April 2019, 119 patients were enrolled in the study. Patients' headache data (MIDAS questionnaire) was collected preoperatively and at a 6 months follow up. Data of 89 patients was available on both stages of collection. Six patients answered the first five questions but not question 6a and 6b *(Appendix 1).* Three patients were excluded due to inadequate tumor histology, namely chordoma, lymphoma and unclear. Fig 2 illustrates the loss of patients from the different stages of data collection.

Fig. 2 Flow chart over study participants.

Variables

Headache

Headache data was quantified using the MIDAS (Migraine Disability Assessment) questionnaire *(*Appendix 1*).* It consists of two parts (1: questions 1-5, 2: questions 6a and 6b). The first five questions address disability due to headache. The scores represent days where the patient completely or partly did not participate in normal daily activities due to headache. The total score can be used to grade the patients' disability caused by headache. The questions 6a and b cover how often and how intensely the patient experienced headache, regardless of how it affected their daily life.

Variables extracted from the MIDAS questionnaire were MIDAS score (0-270) as well as the answers from questions 6a and 6b. The MIDAS score is the number of days collected from questions 1-5, ignoring 6a and 6b. Questions 6a (0-90) and 6b (0-10) were analyzed separately.

The MIDAS score is traditionally used to grade the patients disability from I: little/no disability (0-5) to IV: severe disability (>20). In this study, a fifth grade was added to separate "no disability" from "little disability". The disability from headache will henceforth be graded as described in Table 1.

Table 1 Grading of disability due to headache, based on the migraine disability assessment (MIDAS) score

Disability	Definition	Midas Score
0	No disability	0
I	Little disability	1-5
II	Mild disability	6-10
III	Moderate disability	11-20
IV	Severe disability	21+

Tumor and patient characteristics

The tumor type was determined according to the result of the histopathological analysis performed on extirpated tumor mass. The following tumor characteristics were retrospectively collected from a radiologist or my own assessments of preoperative MRIs, and documented as present or absent: suprasellar extension, chiasm compression and invasion of cavernous sinus. Tumor size was classified as <1 cm or >1 cm in diameter as it represents the boundary where microadenomas are separated from macroadenomas. As non-adenomas were also classified using these measurments, tumor size is not referred to as micro- or macroadenoma.

Sex was recorded as female/male. Age was recorded and divided into the categories <45, 46-60, 61-70, and 71-85 for the analyses.

Statistical analyses

All data was analyzed in Microsoft Excel 14.6.1 and IBM SPSS version 25.0.0.0. Descriptive statistical methods, such as cross tables and charts, were used for the analysis of all patient data, as well as the comparisons between categories and of the headache severity over time. The Wilcoxon signed rank test was used to test for significance of difference in headache data over time. All categorical variables were tested for correlations using Chi-squared tests. A model for the likelihood of headache was derived through logistic regression. The probability of headache, depending on observations x_1, x_2 , was calculated using the following formula: $p = 1-(1/(1+exp(\beta_0+ \beta_1*x_1- \beta_2*x_2))$, where β_0, β_1, β_2 are coefficients given by the logistic regression model.

Ethics

Longitudinal patient data was collected as part of the GoPT-study approved by the Ethical Review Board in Gothenburg, Sweden, and conducted according to the 1964 Declaration of Helsinki. All patients included in this study have signed an informed consent to their medical records being used for research purposes. All data was depersonalized in the analyses.

Results

Table 2 Patient characteristics at baseline, n=119.

Characteristic	Value (%)
Mean age, range	58 ± 15, 19-85
Sex	
Female	59 (49.6)
Male	60 (50.4)
Tumor characteristics	
<1 cm	12 (10.1)
>1 cm	107 (89.9)
Suprasellar extension	103 (86.6)
Chiasm compression	90 (75.6)
Invasion of cavernous sinus	86 (72.3)
Histology	
Non functioning pituitary adenoma	77 (64.7)
Growth hormone	17 (14.3)
Corticotrophin	7 (5.9)
Craniopharyngeoma	6 (5.0)
Prolactinoma	3 (2.5)
Other*	9 (7.4)
Disability based on MIDAS score	
0 0: no disability	77 (64.7)
1-5 I: little disability	6 (5.0)
6-10 II: mild disability	4 (3.4)
11-20 III: moderate disability	4 (3.4)
>20 IV: severe disability	28 (23.5)
6a. On how many days in the last 3 months did you have a headache?	
0 days	44 (38%)
1-90 days	72 (62%)
6b. On a scale of 0 - 10, on average how painful were these headaches?	
Median (IQR)	3 (5)

IQR = Interquartile range
**Langerhans cell, Oncocytoma, Pituicytoma, TSH, Cyst*

Patient and tumor characteristics contributing to headache that negatively affects daily life

72 patients (62%) reported experiencing headache at least once in the three months prior to surgery (MIDAS question 6a). 42 patients (35%) reported headache related disability, defined as a MIDAS score >0. This means that at least for one day in the three months prior to surgery, productivity in normal daily activities was reduced or lost due to headache.

There was no statistically significant correlation between suprasellar extension, compression of the optic chiasm, invasion of the cavernous sinus, hormone production, tumor histology (Fig. 3) and disability deriving from headache (Table 3)**.** Tumor size <1 cm was significantly associated with disability from headache (p=0.016) as well as with hormone production (p<0.001). There was, however, no significant correlation between disabling headache and hormone producing tumors (p=0.159). 66.8% of patients with tumor size <1 cm had headache related disability compared to 31.8% of patients with tumor size >1 cm (Fig. 4).

Statistically significant correlation between female sex and disabling headache (p=0.018) as well as between younger age and disabling headache (p <0.001) was found.

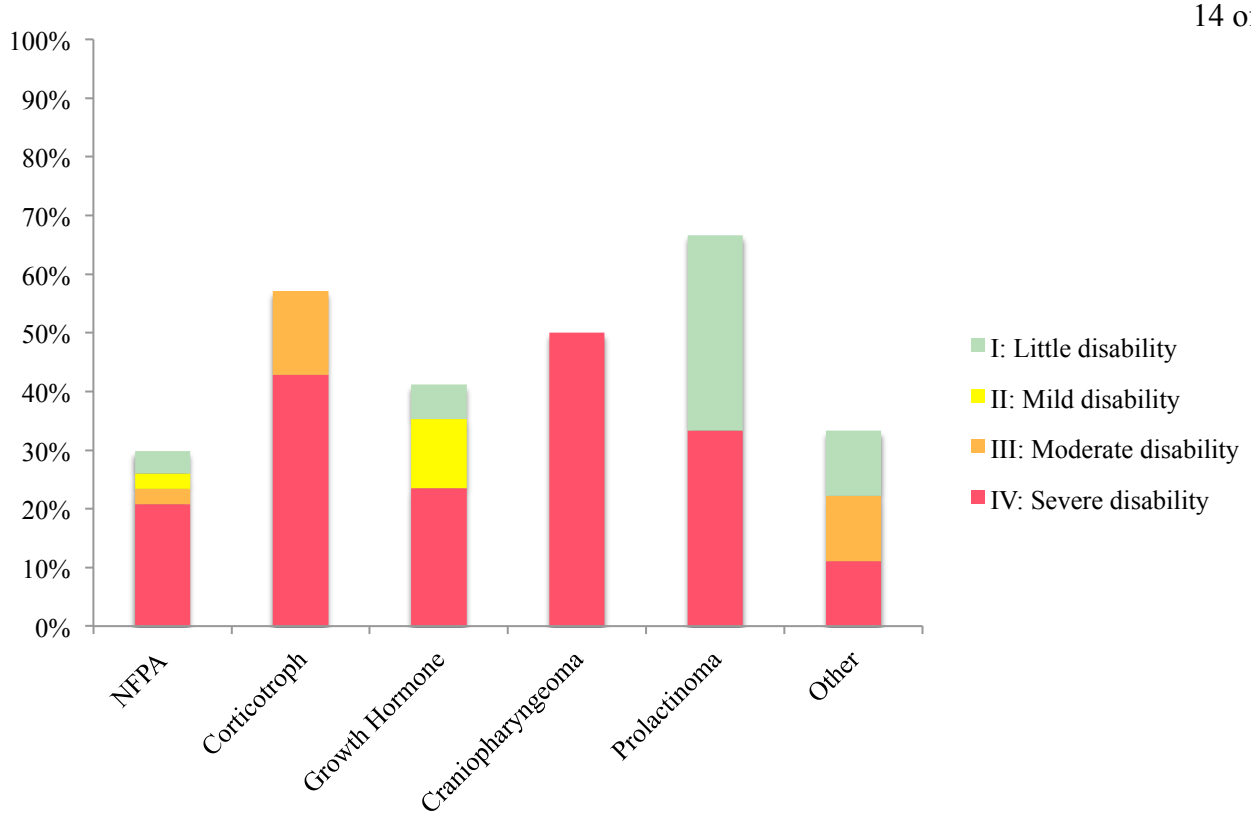

Fig. 3 Distribution of headache related disability according to tumor histology.

NFPA = Non functioning pituitary adenoma

A logistic regression model was made including sex (male=0, female=1) and tumor size (0=<1 cm1=>1 cm) as independent variables. These were the only predictor variables without collinearity with each other and simultaneous presence of ($\chi 2$) correlation to the outcome variable. The dependent variable was headache related disability (no=0, yes=1). Between 8.2 and 11.2% of variance in the dependent variable could be explained by this model. The percentage of accuracy in the classification was 68.1%. The logistic regression model was significant: $\chi 2(2, n=119)=10.15$, $p=0.006$. It gives a female with a tumor <1 cm a 73.2% probability of disabling headache whereas a male with a tumor >1cm in size has a probability of 22.9%.

Among the NFPAs (n=77), one tumor (1.3%) respected the diaphragm sella and was <1 cm in size. Six tumors (7.8%) did not compress the optic chiasm. Analyzing NFPAs alone, disabling headache was significantly associated with tumors *not* compressing the optic chiasm (p=0.04).

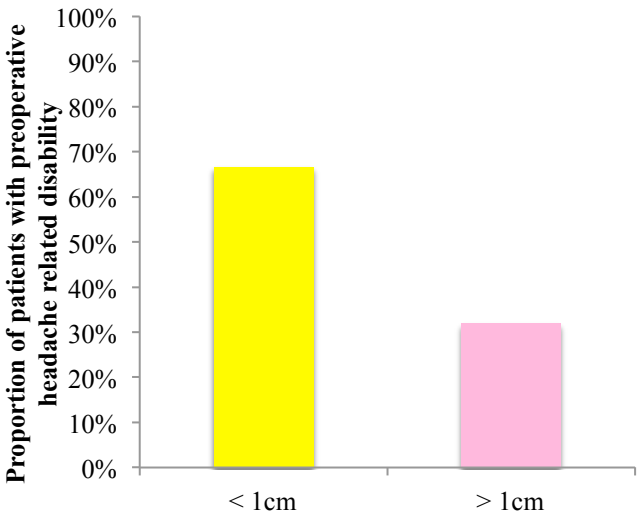

Fig. 4 Distribution of headache related disability according to tumor size </> 1cm

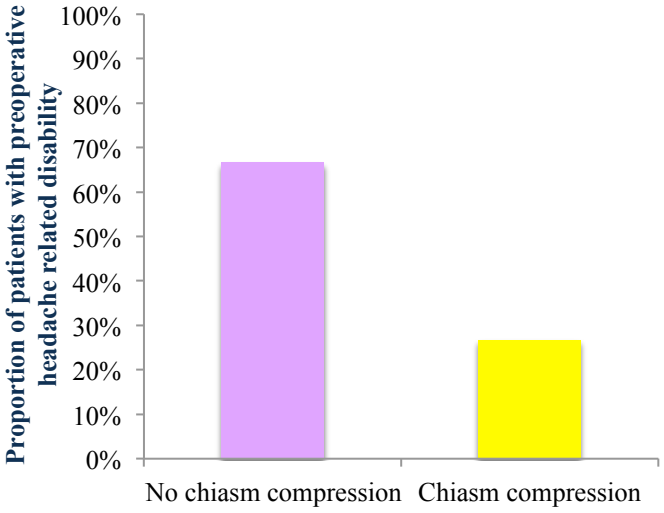

Fig. 5 Relationship between headache related disability and chiasm compression in patients with non functioning pituitary adenoma

26% of patients with chiasm compressing NFPAs suffered from headache related disability compared to 66.7% of patients with non-chiasm compressing NFPAs (Fig. 5). Suprasellar tumor growth, invasion of the cavernous sinus and tumor size (</>1 cm) had no significant association to disabling headache (Table 3).

Transsphenoidal surgery effect on headache related disability

89 patients completed the MIDAS questionnaires both preoperatively and on a six months follow up. 31 patients (34.8%) reported disability due to headache preoperatively. By the six months follow up, 29 patients (32.5%) claimed headache related disability. Of the patients with disabling headache preoperatively, ten patients reported resolution (score=0) at the six months follow up. Ten patients had a worsened score and another 11 experienced relief but not resolution. Eight patients with no disability from headache preoperatively reported disability from headache at the follow up. In conclusion, 21 patients had an improved MIDAS score with a total decrease of 445 days whereas 18 patients worsened by a total of 335 days. Neither the difference in the disability grade nor the total score had any statistical significance (p=0.175, p=0.443).

Table 3 Distribution of patients with or without disability from headache according to tumor histology, hormone production yes/no, size </>1 cm, chiasm compression, suprasellar growth, invasion of the cavernous sinus, sex and age. n=119.

Tumor characteristic n (%within tumor c.)	n=	No disability (MIDAS score=0)	Headache related disability (MIDAS score>0)	Pearson Chi-Square sig. p=
Non functioning pituitary adenoma	77	54 (70.1%)	23 (29.9%)	0.468
Corticotroph	7	3 (42.9%)	4 (57.1%)	
Growth Hormone	17	10 (58.8%)	7 (41.2%)	
Craniopharyngeoma	6	3 (50%)	3 (50.0%)	
Prolactinoma	3	1 (33.3%)	2 (66.7%)	
Other	9	6 (66.7%)	3 (33.3%)	
Not hormone producing	91	62 (68.1%)	29 (31.9%)	0.159
Hormone producing	28	15 (53.6%)	13 (46.4%)	
No invasion of cavernous sinus	30	17 (56.7%)	13 (43.3%)	0.236
Invasion of cavernous sinus	86	59 (68.6%)	27 (31.4%)	
Size <1 cm	12	4 (33.3%)	8 (66.7%)	0.016
Size >1 cm	107	73 (68.2%)	34 (31.8%)	
No suprasellar growth	16	7 (43.8%)	9 (56.3%)	0.059
Suprasellar growth	103	70 (68%)	33 (32%)	
No chiasm compression	28	14 (50%)	14 (50%)	0.052
Chiasm compression	90	63 (70%)	27 (30%)	
Female sex	59	32 (54.2%)	27 (45.8%)	0.018
Male sex	60	15 (25%)	45 (75%)	
Age <45 years	26	9 (34.6%)	17 (65.4%)	<0.001
Age 46-60 years	36	19 (53.8%)	17 (47.2%)	
Age 61-70 years	30	25 (83.3%)	5 (16.7%)	
Age 71-85 years	27	24 (88.9%)	3 (11.1%)	

MIDAS = Migraine disability assessment

Table 4 Only non functioning pituitary adenomas: Distribution of patients with or without disability due to headache by patient and tumor characteristics. n=77.

Tumor/patient characteristic	n=	No disability (MIDAS score=0)	Headache related disability (MIDAS score>0)	Pearson Chi-Square sig. p=
No invasion of cavernous sinus	12	7 (58.3%)	5 (41.7%)	0.306
Invasion of cavernous sinus	63	46 (73%)	17 (27%)	
Size <1 cm	1	0 (0%)	1 (100%)	0.123
Size >1 cm	76	54 (71.1%)	22 (28.9%)	
No suprasellar growth	1	0 (0%)	1 (100%)	0.123
Suprasellar growth	76	54 (71.1%)	22 (28.9%)	
No chiasm compression	6	2 (33.3%)	4 (66.7%)	0.040
Chiasm compression	71	52 (73.2%)	19 (26.8%)	
Female	37	22 (59.5)	15 (40.5%)	0.049
Male	40	32 (80%)	8 (20%)	
<45 years	11	5 (45.5%)	6 (54.5%)	0.004
46-60 years	22	11 (50%)	11 (50%)	
60-70 years	21	17 (81%	4 (19%)	
71-85 years	23	21 (91.3%)	2 (8.7%)	

MIDAS = Migraine disability assessment

Looking at patients with baseline disability (score >0) alone (n=31), a significantly reduced disability grade (p=0.003) could be noted (Fig. 6). The score, however, was not significantly reduced (p=0.09). Looking at patients with NFPAs or hormone producing adenomas separately, neither group had a significantly reduced MIDAS score or grade.

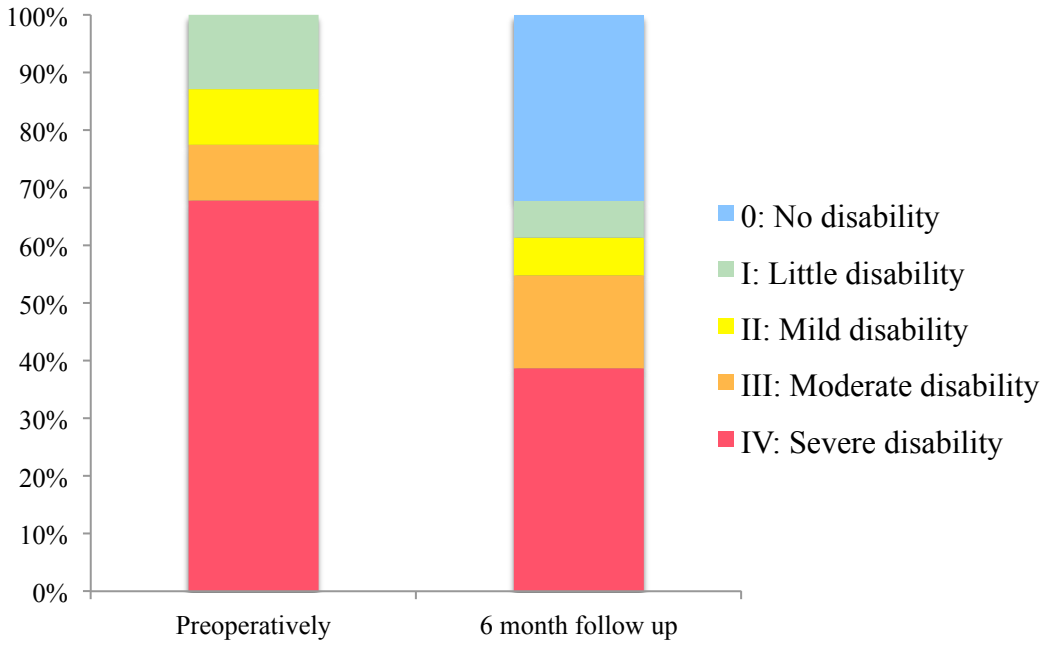

Fig. 6 Headache related disability in the patients with preoperative headache related disability

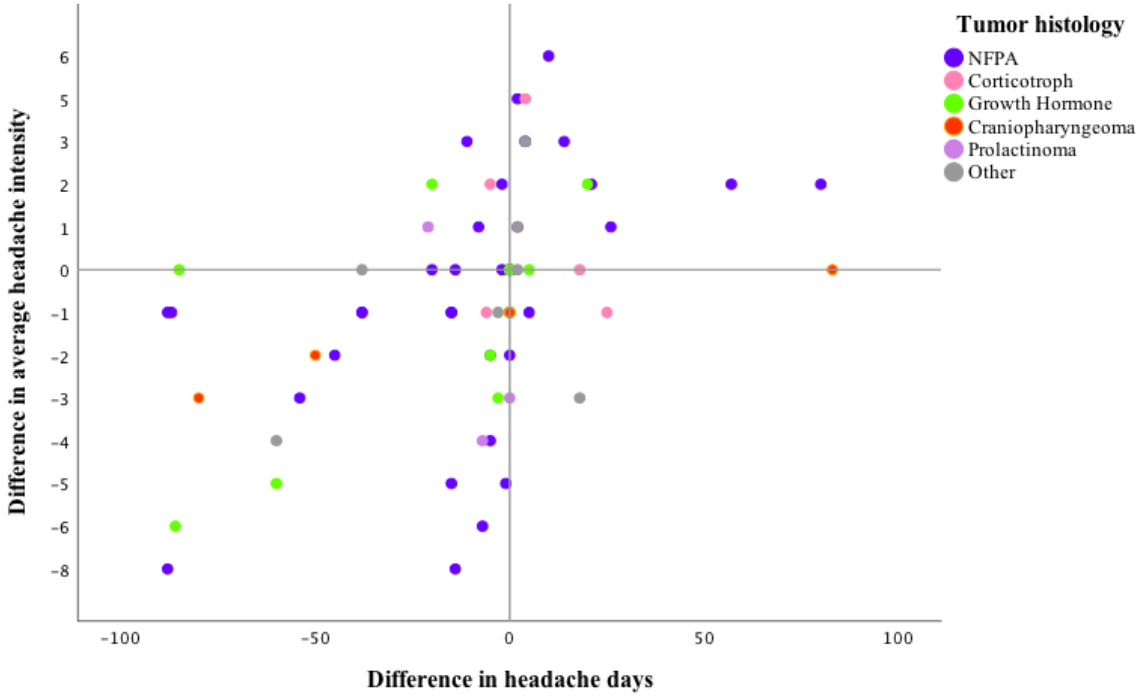

Fig. 7 Difference in headache frequency and intensity six months after transsphenoidal surgery, by tumor histology

NFPA = Non functioning pituitary adenoma

Transsphenoidal surgery effect on headache frequency and intensity

83 patients answered MIDAS questions 6a and 6b regarding headache frequency and average intensity preoperatively and at the six months follow up. 29 patients (34.9%) reported 0 days headache whereas seven patients (8.4%) reported 90 days (meaning headache every single day). On the six months follow up, 31 patients (37.3%) reported zero days of headache and four (4.8%) reported 90 days. The median frequencies were 5 (30)* and 3 (10) respectively, and significantly reduced (p=0.013). Headache intensity was not significantly reduced: median preoperative 3 (6)* and on follow up 2 (5) (on a scale of 0-10). These results are plotted in Fig. 7.

**Interquartile range, IQR*

Relation between postoperative reduced headache and tumor characteristics

Reduced headache frequency and intensity (visualized in the lower left quadrant of Fig. 7) did not significantly correlate to either compression of optic chiasm, tumor size <1 cm, suprasellar growth, invasion of the cavernous sinus or tumor histology. Reduced headache related disability defined as a lower MIDAS score correlated with tumor size <1 cm (p=0.003) (Fig. 8) and tumors not compressing the optic chiasm (p=0.047). No significant association between a lower MIDAS score and suprasellar growth, hormone producing tumors, tumor histology, nor invasion of the cavernous sinus was found (Table 5).

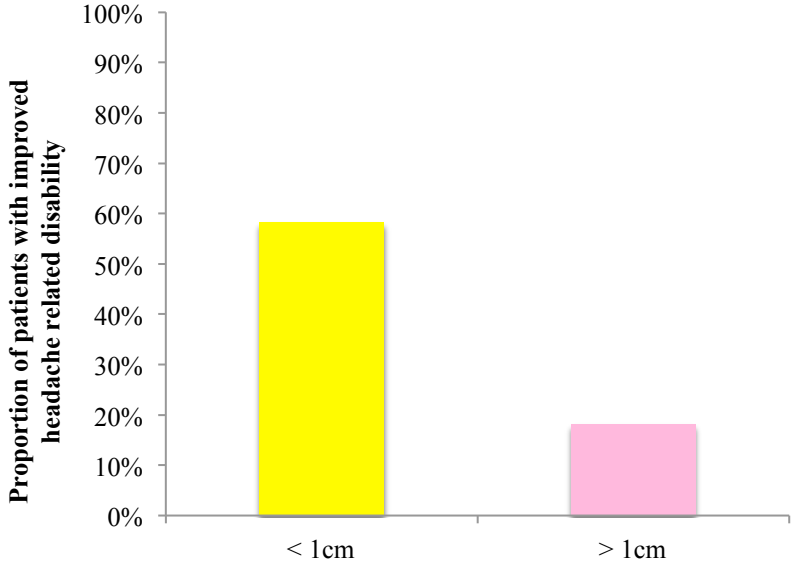

Fig. 8 Relationship between reduced headache related disability and tumor size </> 1cm

Table 5 Improved (n=21) versus worsened (n=18) or unchanged (n=50) headache related disability and patient/tumor characteristics. *Chi-squared tests were performed with unchanged and worsened patients merged in to one group so as to have a dichotomous variable(0=Improved, 1=Unchanged or worsened).*

Tumor characteristic n (%within tumor c.)	n=	Lower MIDAS score	Unchanged MIDAS score	Higher MIDAS score	Pearson Chi-Square sig. p=
Non functioning pituitary adenoma	54	11 (20%)	37 (67.3%)	7 (12.7%)	0.655
Corticotroph	6	3 (50%)	1 (16.7%)	2 (33.3%)	
Growth Hormone	14	4 (28.6%)	7 (50%)	3 (21.4%)	
Craniopharyngeoma	4	1 (25%)	1 (25%)	2 (50%)	
Prolactinoma	3	1 (33.3%)	1 (33.3%)	1 (33.3%)	
Other	7	1 (14.3%)	3 (42.9%)	3 (42.9%)	
Hormone producing	24	8 (33.3)	10 (41.7%)	6 (25%)	0.202
Not hormone producing	64	13 (20%)	40 (61.5%)	12 (18.5%)	
Invasion of cavernous sinus	61	12 (19.4%)	39 (62.9%)	11 (17.7%)	0.136
No invasion of cavernous sinus	26	9 (34.6%)	11 (42.3%)	6 (23.1%)	
Size <1 cm	12	7 (58.3%)	2 (16.7%)	3 (25%)	0.002
Size >1 cm	76	14 (18.2%)	48 (62.3%)	15 (19.5%)	
Suprasellar growth	74	15 (20%)	46 (61.3%)	14 (18.7%)	0.069
No suprasellar growth	14	6 (42.9%)	4 (28.6%)	4 (28.6%)	
Chiasm compression	63	11 (17.2%)	41 (64.1%)	12 (18.8%)	0.047
No chiasm compression	24	9 (37.5%)	9 (37.5%)	6 (25%)	
Female	42	12 (28.6%)	19 (45.2%)	11 (26.2%)	0.322
Male	46	9 (19.1%)	31 (66%)	7 (14.9%)	
<45 years	24	11 (45.8%)	6 (25%)	7 (29.2%)	0.008
46-60 years	26	6 (23.1%)	13 (50%)	7 (26.9%)	
60-70 years	22	4 (18.2%)	15 (65.2%)	4 (17.4%)	
71-85 years	16	0 (0%)	16 (100%)	0 (0%)	

MIDAS = Migraine disability assessment

Discussion

The present study primarily found that patients suffering from headache related disability experienced a reduction thereof six months postoperatively. Further, that female patients and patients with tumors smaller than 1 cm in diameter had a higher probability of disabling headache than their counterparts. It was also observed that the small tumors were associated to postoperative improvement of headache to a greater extent.

Prevalence of headache in the sample compared to the general population

The analysis material at hand was comprised of 119 patients of which 62% reported headaches at least once in three months. In a Swedish headache prevalence study performed by SIFO in 2001, 1668 Swedish people were asked whether they had recurring headaches, to which 62% answered with yes[4]. This result is in line with the findings in our study population (question 6a) *(*Appendix 1*)*. Reviews of global headache prevalence studies show that results are extremely varied. In an article published in 2010, reviewing the prevalence of current headaches all over Europe, the mean prevalence was calculated to be 53%, with results ranging from 16.7% - 96%[22,25,31]. Regarding patients with pituitary tumors, the headache prevalence's reports range from 37-70%[1,18]. Because of the inconsistencies in quantification methods, it is not possible to make a credible headache prevalence comparison between the general population and patients with pituitary tumors. Further, there are currently no means to compare the impact and severity of headache between these populations.

Reasons for more headache related disability in patients with tumors of <1 cm in size

The population in this study was collected from a surgical context. For this reason, merely one of the small tumors in the sample were hormone producing. We cannot distinguish between hormonal/biochemically derived headache and mass effect from the tumor. Patients with NFPAs that did not compress the optic chiasm had, however, significantly more disabling headache

compared to patients with NFPAs that compressed the chiasm. This indicates that there is a physical component to the relationship between small tumors and headache.

One of the most accepted theories of how brain tumors give rise to pain is through increased intracranial pressure[34]. In this case, the tumor is situated in the sella turcica, limited cranially by the diaphragm sellae. A large tumor has broken these limitations and expands on bigger grounds, preventing an increased intrasellar pressure. As long as a tumor is still captured by the cerebral membranes lining the sella, the pressure inside (ISP) can build. There are few studies focused on the relationship between ISP and headache. Gondim et al. found pituitary adenomas with enlarged and intact sellas (Hardy-Vezina class II), to be associated with a much higher ISP compared to tumors with either no impact on sella or breaking sellar boundaries[13]. Baha M Arafah et. al. found a significantly higher ISP in patients with headache[2] while Pereira-Neto et. al. found no such correlation[24].

Intuitively, a faster growing tumor would be more likely to cause a raised ISP. One study found highly proliferative tumors (Ki-67%- labeling index >3) to be associated with headache[28]. The clinical implications of this knowledge are, however, not obvious, as proliferation rate is not known until postoperatively from tumor samples.

Surgery as treatment for headaches

We do not know with certainty whether the headaches experienced by the patients in our study were attributed to the tumors, latent hereditary and triggered by the tumors, or were not related to the tumors at all. Regardless of that, the results of the present study suggest that patients with the unfortunate combination of disabling headache and pituitary tumor seem to see relief through surgery. Including all patients in the sample, it has to be considered, however, that some patients actually worsened in or aquired headache after transsphenoidal resection of the tumor. The reason why some patients experience a worsening in headache six month after surgery is not evident. It would be expected that pain secondary to wound healing in the surgical field should not be present at that time, but supposing a pituitary mass can trigger migraine in a patient with a latent

predisposition, a surgical manipulation in the same area might have the same effect. As in the case of preoperative headache, postoperative headache can be assumed to depend on a variety of mechanisms.

Since the patients in this study had indications for surgery in addition to headache, a reduction or increase of headache postoperatively can be considered a bonus or "necessary evil". Cumulate results, including ours, reject the hypothesis that a large and invading tumor would be more likely to cause headache. This strengthens the incentive to investigate whether headache in some cases may be an appropriate indication for surgery, as currently, merely large tumors are likely to eventually compress the optic chiasm or pituitary gland, hence providing a ticket to the operating room, whereas small tumors are not.

Choice of headache quantification method

The MIDAS questionnaire was developed in order to monitor symptoms and evaluate treatment efficacy in patients with migraine. It is an upgrade of a similar questionnaire called the HIT-6[30]. The latter, and to some extent also MIDAS, has been used for quantitative evaluation of headache in other patient categories such as the present one, due to the lack of of other alternatives. The suitability is questionable. For one, the original grading allows up to five out of 90 days headache-caused absence from work in the lowest category of disability. This might be acceptable in patients with chronic migraine. In case of a disabling headache being a refractory condition caused by something else (such as a pituitary tumor), it might, however, not be ideal. Researchers in the area of pituitary tumors and headache have mentioned the need of a headache quantification tool developed specifically for patients with pituitary tumors[5,15].

Other methodological considerations

As mentioned above, the patients included in the study already had some operation indication. This is appropriate when investigating possible headache reduction through surgery. For the evaluation of headache severity, prevalence and possible mechanisms causing headache, it would, however, be valuable to also include patients with PAs that are not indicative for surgery.

The size of the cohort was adequate and the variables analyzed were relevant for the purpose of the study. A few of the Chi-squared analyses did not reach the recommended minimum of five patients. This is accounted for in tables 3-5.

Furthermore, we have not taken into consideration if the surgery within the frame of the study was the first, or one out of several reoperations. It is possible that only one follow up was a blunt outcome measure, especially with a known high recidivism frequency.

Participation in the study was high and the loss of data negligible (Fig. 2). Except for MIDAS as headache quantification tool, discussed above, the methods for data collection can be assessed as adequate.

Conclusion

The traditional theories that invasive pituitary tumors would cause headache through compression of pain-sensitive structures around the sellae could not be confirmed in the present study. On the contrary: our finding suggests that small tumors are associated to headache and reduction of headache postoperatively. Further studies could preferably investigate prevalence of headache in patients with small pituitary tumors and possible headache-causing mechanisms, such as increased intrasellar pressure. More research on whether endoscopic transsphenoidal surgery effectively reduces headache in this patient category would also be beneficial.

Based on the results from this study, headache alone as an indication for surgery can not be recommended. Future research, as mentioned above, should have the objective to identify a patient type for which headache as an indication for transsphenoidal surgery would be a cost-effective and medically justifiable extension to current treatment guidelines.

Furthermore, the development of a headache quantification tool adapted for patients with pituitary tumors would be beneficial, both for future studies and in clinical practice when managing headache in these patients.

Populärvetenskaplig sammanfattning

Hypofystumörer, transsphenoidal resektion och huvudvärk – en prospektiv kohortstudie

En av de vanligaste typerna av tumör som drabbar hjärnan är en så kallad hypofystumör. Det är en tumör som utgår från eller är lokaliserad vid en liten körtel under hjärnan som kallas för hypofysen. Hypofysens uppgift i den friska kroppen är att styra produktionen av hormon från diverse organ. Lokalen för hypofysen är väldigt specifik och omgiven av känsliga strukturer som kärl och nerver. På grund av hypofysens lokal och funktion kan en liten tumör här ha en kraftig symptombild, antingen i form av hormonrubbning eller i typfallet synfältsbortfall för att den trycker på synnerven. I den här patientgruppen är det också vanligt med huvudvärk, dock inte klarlagt om det egentligen är vanligare än hos normalbefolkningen, och det är mycket svårt att veta om huvudvärken hos en sådan här patient beror på en hypofystumör eftersom den ofta ter sig precis som andra "normala" huvudvärkstillstånd.

Den här forskningen syftar till att kartlägga hur vanlig huvudvärk är bland patienter med hypofystumör, samt att hitta samband mellan tumör- och patientrelaterade faktorer och huvudvärk. Därutöver att utröna om en operation med borttagning av tumören genom näsan hjälper mot huvudvärken. I förlängningen skulle sådan kunskap kunna leda till att huvudvärk hos en viss typ av patient leder till att man bestämmer sig för att operera patienten. I nuläget är huvudvärk i sig inte en indikation för operation, utan det krävs andra symptom från tumören för att man ska välja att operera bort den. Den här studien är genomförd på data från 119 patienter som alla har opererat bort en hypofystumör med hjälp av titthålsteknik via näsan. Patienternas huvudvärk före och 6 månader efter operation har omvandlats till poäng med hjälp av ett frågeformulär som kallas MIDAS. Den här datan har jämförts med andra faktorer hos patienten som typ av tumör, storlek på tumör, tumörens växtsätt, patientens ålder och kön.

Resultaten visade att tumörer med en diameter <1 cm i större utsträckning var kopplade till huvudvärk än tumörer med diameter >1cm. Det var också patienterna med små tumörer som upplevde störst förbättring av operation. Kvinnorna hade svårare huvudvärk än männen. Av de

patienter som hade handikappande huvudvärk innan sin operation var det 68% (21 av 31) som blev bättre, en statistiskt signifikant förbättring. Såg man på hela gruppen så var förbättringen av huvudvärk inte statistiskt signifikant. 18 patienter (20%) var sämre i sin huvudvärk 6 månader efter sin operation.

De här resultaten är relevanta för att de bekräftar vad tidigare studier på området har pekat på: att stora tumörer inte ger mer huvudvärk än små. Däremot så verkar det som att patienter med små tumörer och huvudvärk kan bli hjälpa av operation. Detta kan vara värt att fortsätta undersöka, eftersom att små tumörer med huvudvärk som enda symptom just nu inte behandlas med operation, då det inte finns tillräckligt med underlag för att hävda att nyttan skulle vara större än riskerna.

Acknowledgements

As I started working on this project I quickly developed a motherly love for the data, which resulted in a slightly unhealthy, yet very effective, working process. It might be the lack of real struggles in my petty life, but providing results to Thomas and Tobias became my true purpose. Feeling like there is a purpose to fulfill is the very best gift, therefore I'd like to formally give thanks to…

… Patients who agreed to participate in the study. Filling out questionnaires is very boring, but you did it and for this I salute you.

… Thomas Skoglund and Tobias Hallén for the reckless move of letting me handle this very much on my own, yet providing spirited guidance in times of distress.

… Johanna Talus for introducing me to the possibility.

… Erika Backlund for keeping me company. I apologize for the frequent distractions.

… Julia Sjöström for Excel-support and repeatedly reminding me that I'm not supposed to be born with complete research and statistics-skills.

… Katarina Gren for emotional support, always.

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Appendices

Appendix 1: The MIDAS questionnaire

___1. On how many days in the last 3 months did you miss work or school because of your headaches?

___2. How many days in the last 3 months was your productivity at work or school reduced by half or more because of your headaches? (Do not include days you counted in question 1 where you missed work or school.)

___3. On how many days in the last 3 months did you not do household work (such as housework, home repairs and maintenance, shopping, caring for children and relatives) because of your headaches?

___4. How many days in the last 3 months was your productivity in household work reduced by half of more because of your headaches? (Do not include days you counted in question 3 where you did not do Household work.)

___5. On how many days in the last 3 months did you miss family, social or leisure activities because of your headaches?

6 A. On how many days in the last 3 months did you have a headache? (If a headache lasted more than 1 day, count each day.)

6 B. On a scale of 0 - 10, on average how painful were these headaches? (Where 0=no pain at all, and 10=pain as bad as it can be.)