

Abstract:

Background: Although headache and pituitary adenoma are two prevalent conditions that may coexist, it has also been postulated that pituitary adenomas may cause secondary headaches that resemble primary headaches. Headache alone is so far a controversial indication for treatment of pituitary adenoma.

Purpose: To gain knowledge about the relationship between pituitary tumours and headache, and possible symptomatic effects of treatment.

Materials and method: Patients diagnosed with or treated for pituitary adenomas in a 10-year period in a single institution were invited to participate in the study. The 208 (86%) included patients underwent structured telephone interviews concerning current and prior headache complaints while type of tumour, endocrine variables, treatment variables, MRI variables and headache history were recorded from medical records. Headache prevalence among patients was compared to identical measures of headache prevalence from a regional population based study in volunteers.

Results: The current cross sectional age and sex-adjusted 1-year prevalence of headache suffering (21%) is significantly lower than the general population (37%) $p < 0.001$. Assessed retrospectively, prevalence of headaches was significantly higher (48%) $p < 0.001$ before being diagnosed with pituitary adenomas than in the general population. With the exception of family history of headache ($p = 0.020$), no associations between headache and measured clinical or radiological variables were identified.

Conclusion: Although patients retrospectively reported relief of headache complaints after treatment current prevalence of headaches among patients harbouring both treated and untreated pituitary adenomas is low compared to the general population. Furthermore, the lack of variables associated with headache suggests that headache alone as a sole indication for treatment of pituitary tumours is still debatable

Relevance:

Patients with pituitary adenomas sometimes suffer from headaches but the biological link between headache and pituitary tumours is not established. Headache is a controversial indication for surgery of pituitary tumours, and an (dose-response) association between headache and pituitary tumours has not yet been found.

Current clinical guidelines for surgery of pituitary incidentaloma (1) nevertheless suggest that surgery be considered for patients suffering from “unremitting headaches”, but objective criteria to select and identify who would benefit from surgery are lacking.

Acknowledgements

I am indebted to my supervisors Erling Andreas Tronvik and Ole Solheim for their excellent guidance and their willingness to share of their vast knowledge.

Thanks to my colleagues for providing me with time to work with the thesis and to my family for their contribution to a great working environment in the living room.

Thanks to endocrinologist Stine Fougner for providing diagnostic codes used by endocrinologists, and lists of patients registered with the diagnosis.

A special thanks to the participants in the study.

Contents

| | | |
|-------|---|----|
| 1 | Theoretical background..... | 1 |
| 1.1 | Headache | 1 |
| 1.1.1 | Primary headaches..... | 1 |
| 1.1.2 | Secondary headaches..... | 1 |
| 1.2 | HUNT | 1 |
| 1.3 | Pituitary adenomas | 2 |
| 1.3.1 | Prevalence | 2 |
| 1.3.2 | Types of adenomas | 3 |
| 1.3.3 | Pituitary tumour apoplexy | 4 |
| 1.3.4 | Current management of pituitary adenomas | 5 |
| 2 | Introduction..... | 7 |
| 3 | Materials and methods | 9 |
| 3.1 | Study design | 9 |
| 3.2 | Study population..... | 9 |
| 3.3 | Data collection..... | 10 |
| 3.4 | Headache assessment..... | 11 |
| 3.5 | Hormone assessment | 11 |
| 3.6 | Radiological assessment | 11 |
| 3.7 | Statistical analysis..... | 11 |
| 3.8 | Ethics | 12 |
| 4 | Results..... | 13 |
| 4.1 | Pituitary adenomas and headache..... | 13 |
| 4.2 | Prevalence of non-acute headache compared to the general population | 14 |
| 4.3 | Type, size or location of pituitary tumour and headache | 14 |
| 4.4 | Does pituitary surgery reduce headache? | 16 |
| 5 | Discussion | 19 |
| 5.1 | Main findings..... | 19 |
| 5.2 | Clinical interpretation | 19 |
| 5.3 | Strengths and weaknesses..... | 23 |
| 5.4 | Implications for future research..... | 24 |
| 6 | Conclusion | 25 |
| 7 | References..... | 27 |
| 8 | Appendix..... | 31 |
| 8.1 | Appendix 1 Patient information/consent | 33 |
| 8.2 | Appendix 2 Questionnaire | 35 |
| 8.3 | Appendix 3 MR variables registration schema..... | 41 |

1 Theoretical background

1.1 *Headache*

Headache is pain located above the orbitomeatal line (2). Headache diagnoses are usually made on the basis of subjective experiences without any objective sign or markers.

Estimated prevalence is dependent of quality of recall, cultural differences and the nature of the question (3).

1.1.1 Primary headaches

The most prevalent primary headaches are migraine and tension type headache. Migraine is a recurrent headache disorder with attacks lasting 4-72 hours. Typical characteristics of the headache are unilateral location, pulsating quality, moderate or severe intensity, aggravation by routine physical activity and association with nausea and/or photophobia and phonophobia (2). Tension type headache is typically bilateral, pressing or tightening in quality and of mild to moderate intensity, lasting minutes to days. The pain does not worsen with routine physical activity and is not associated with nausea, but photophobia or phonophobia may be present (2).

1.1.2 Secondary headaches

The International Classification of Headache Disorders (ICHD-III) includes a list of secondary headaches. A new headache occurring together with another disorder recognized to be capable of causing it, is always diagnosed as secondary (2). Headache attributed to space-occupying intracranial tumours in general is usually progressive, worse in the morning and aggravated by Valsalva-like manoeuvres. Headache due to pituitary tumours may be associated with hypothalamic or pituitary hyper- or hyposecretion, and can be associated with disturbed temperature regulation, abnormal emotional state and/or altered thirst or appetite (2).

1.2 *HUNT*

The Nord-Trøndelag Health Study (The HUNT Study) is a cross-sectional comprehensive health study conducted in all inhabitants 20 years and older, in a Norwegian county with 134.443 inhabitants per 2014 (4). The study has been conducted three times, and a fourth is under preparation. The first study conducted between 1984 and 1986 did not include headache questions. The second HUNT Study (HUNT 2) was conducted between 1995 and 1997, and 51 383 subjects completed a headache questionnaire, and revealed an overall age-adjusted 1-

year headache prevalence of 46% in women and 30% in men, a total prevalence of 38% (5). The third HUNT Study (HUNT 3) was conducted between 2006 and 2008, and 39 690 individuals 20 years and older answered the Head-HUNT survey (6). The overall age-adjusted 1-year headache prevalence was 43% in women and 30% in men, a total prevalence of 37%. Thus, after 11 years there was no significant differences from the HUNT 2 to the HUNT 3 study regarding the prevalence of all headaches combined (37.7% vs 37.4%; $p=0.36$) (6). Individuals who answered “yes” to the question “Have you suffered from headache during the last 12 months?” were classified as headache sufferers (5). Answering the subsequent 13 headache questions enabled diagnosing migraine according to the International Classification of Headache Disorders (ICHD-II) (6, 7). The headache questionnaire and questionnaire-based diagnoses have previously been validated (8, 9).

1.3 Pituitary adenomas

1.3.1 Prevalence

In 95% of cases, pituitary tumours occur sporadically and are benign. Pituitary adenomas are frequent and in many cases clinically silent. The majority of tumours grow slowly and rather predictably, with long and often increasing doubling times. About half to one third of all pituitary adenomas are non-functioning, i.e. do not produce hormones (10). Of hormone secreting tumours, prolactinomas are the most common, accounting for 25-41% of all pituitary adenomas (11). Growth hormone producing tumours represent 10-15%, and approximately 10% are adrenocorticotrophic hormone (ACTH) producing adenomas (12). Pituitary adenomas affect both genders equally, but there are differences in frequencies between genders for certain subtypes, as for instance ACTH-producing adenomas and prolactinomas are more common in women (10). The overall estimated prevalence of adenomas in the population is 16.7%, but in routine autopsies they can be discovered in up to 22.5% (11).

The historical lack of mandatory reporting of benign brain tumours may have led to an underestimation of the prevalence of pituitary adenoma in cancer registries (13) and many tumours are never histologically verified. An accurate estimate of the prevalence is therefore not available (14). More available and improved imaging techniques have increased the incidence rates of pituitary adenomas (15), and prevalence studies in Europe and in the USA report of increasing prevalence (13, 16, 17).

1.3.2 Types of adenomas

Pituitary adenomas are classified depending on their size into microadenomas (<1cm) and macroadenomas (≥1cm). This classification is supplemented by immunochemistry (cell type, hormone receptors) into functional (active) or non-functional (or silent/inactive) adenomas based on their ability to produce and secrete mature hormones (12).

Tumours are still considered clinically active only if the amount of hormone secreted leads to excessive levels in the blood (10, 18). Incidentaloma is an incidentally discovered pituitary adenoma from imaging performed for an unrelated cause (19).

1.3.2.1 Non-functional adenomas

When diagnosed, the majority of the non-functional adenomas are macroadenomas, as there are no syndrome or hormone disturbances to bring them to medical attention when they are smaller (18). Larger tumours compress the normal pituitary gland and patients may acquire hormone deficiencies. Early symptoms of hormone deficiencies, or secondary hyperprolactinemia (elevated level of prolactin in the blood) due to the mass effect of the tumour upon the pituitary stalk, are fatigue, low libido or erectile dysfunction, oligomenorrhoea or amenorrhoea, anaemia, headache and visual problems (10, 18, 19). Headache is the most common symptom. Visual symptoms are present in 50% of patients with macroadenomas (19).

Surgery remains the primary treatment, and the goals of the treatment are to relieve the mass effect, restore pituitary function, and to obtain a tissue diagnosis (10). 70-80% of patients experience significant improvement in visual function, and it has been reported that nearly 100% experience resolution of headaches postoperatively (10).

1.3.2.2 Functional adenomas

Prolactin secreting adenomas (Prolactinomas)

Prolactinoma is the most commonly diagnosed pituitary adenoma. Some regress spontaneously, many stay unchanged for many years, and a few expand to cause local mass effects. The individual clinical picture of hyperprolactinemia is determined by the gender and age of the patient and the tumour size (18).

Effective medical treatment is available and is the first line management. Dopamine agonists normalize prolactin levels, control galactorrhea, restore reproductive function, and decrease tumour sizes in most patients (10, 20).

GH secreting adenomas (Acromegaly)

Clinically, acromegaly is characterized by soft tissue swelling, excessive skeletal growth, sweating, reduced life expectancy and a reduced quality of life (21), a result of chronic overproduction of growth hormone over years (22). The majority of the patients with acromegaly harbour pituitary macroadenomas (18).

Surgery is the preferred primary treatment (10). Preoperative tumour shrinkage improves surgical cure rates, and pre-surgical treatment with somatostatin analogues for 6 months is used in most macroadenomas (23-25). The reduction in tumour volume is usually modest. Medical therapy is also indicated in patients who do not achieve biochemical cure after resection or have disease recurrence (22).

ACTH-secreting adenomas (Cushing's syndrome)

The clinical manifestations associated with hypercortisolemia are variable and differ widely in severity. Signs and symptoms may include gross obesity of the trunk with wasting of the limbs, facial rounding and plethora, hirsutism with frontal balding, proximal muscle weakness, vertebral fractures, hypertension, diabetes mellitus, anxiety/depression, acne, easy bruising, loss of libido and menstrual irregularity (22).

Surgery is the treatment of choice and the large majority (89%) are microadenomas (10). In 25-45% of the cases MRIs do not demonstrate identifiable lesions, and explorative surgery may be carried out (10). Although, surgery is the primary treatment, 10-30% of patients unfortunately fail to achieve remission after initial surgery, and a similar percentage may recur over time (22). Stereotactic radiosurgery or adrenalectomy are treatment alternatives if remission is not achieved (18).

1.3.3 Pituitary tumour apoplexy

Pituitary tumour apoplexy is haemorrhage or infarction in a pre-existing pituitary adenoma (26, 27). It is uncommon, and is characterized by sudden onset of severe headache (92-100%) nausea and vomiting, visual field disturbances, diplopia, impaired consciousness, or nonspecific symptoms (28) that resolve over some days or weeks, (27). Pituitary tumour apoplexy can be fatal as a result of hypopituitarism and cortisol deficiency, and a correction of any hormone deficit is required before surgery (19). If headache is the predominant symptom it can be advisable to await natural recovery (18). The debate regarding optimal management strategy still persists (27).

1.3.4 Current management of pituitary adenomas

Current management of pituitary adenomas range from a conservative expectant approach (wait and scan), to treatment with medical drugs, surgery, and/or radiotherapy.

MRI is the method of choice to detect and monitor pituitary adenomas, and image surveillance is usually required for life in patients with non-functional adenomas. MRI can provide precise information about the size, location, and extent and indicate the nature of a lesion. To monitor functional adenoma hormonal laboratory parameters are used (21).

Therapeutic approaches depend on patient age, comorbidity, symptoms, tumour growth, tumour type, tumour size and invasiveness. The choice of treatment modality is determined by several factors including: relief of mass effect, treatment of hormone excess or restoration of hormone deficits, prevention of tumour regrowth, and minimizing long-term morbidity and mortality (22).

Asymptomatic patients with non-functioning pituitary adenomas may be candidates for conservative management (22), and a suggested follow-up regime is available in “The endocrine society clinical practice guideline” (1).

Active treatment is generally reserved for symptomatic adenomas causing visual field defects due to compressing of the optic nerves or other cranial nerve deficits, hormone secreting adenomas causing endocrine disturbances, or growing adenomas causing progressive pituitary failure (endocrine deficiency) or approaching the optic nerves (1).

Transsphenoidal surgery (TSS) is the preferred surgical route in most cases today, and is used in about 97% of all surgery of pituitary adenomas (29). It is the least traumatic route, without visible scars, associated with lower morbidity and mortality than transcranial routes, and only a short hospital stay and a brief recuperative period is needed (18). The 30-day mortality rate for patients operated for pituitary adenomas in Norway after 1990 is 0.6% (30). Surgical debulking is done to improve subsequent response to medical therapy when complete surgical resection is not feasible or safe (31).

Due to the high prevalence of both headache and pituitary tumours, both may coexist incidentally, and it is still controversial if pituitary tumours cause headache and if surgical removal is effective for symptom relief. Reported improvements could be influenced by the considerable placebo responses associated with surgery.

2 Introduction

Headache is a prevalent disorder; the 1-year prevalence of “headache suffering” is 37% (6). The International Classification of Headache Disorders (ICHD-III) defines primary and secondary headaches. The mechanisms responsible for the headache due to pituitary tumours are said to be caused by “space-occupying intracranial tumours” or “pituitary hyper- or hyposecretion” of hormones (2). The prevalence of pituitary adenomas increases with age and improved diagnostic method. A systematic review found a pooled prevalence of 16.7% across studies (11). The possible relationship between pituitary adenomas and headache remains controversial as both conditions may coexist by chance due to the high prevalence of both disorders. The evidence of an association between pituitary adenomas and headache is generally weak and headache alone is still a controversial indication for pituitary surgery (1), despite rather good results in published series (15). Surgical removal of a pituitary adenoma with the intention to treat headache is seldom carried out in Norway. The reason for this is the lack of evidence of a directly related treatment effect on the one hand, and the known risk of perioperative complications on the other (30). Headaches in patients with pituitary adenomas may vary from mild to severe, and the severity is seemingly not related to tumour size (32, 33). Since these tumours usually grow slowly and can become quite large before they are discovered, possible associated headaches may be present for many years. On the other hand, many patients with very large tumours are surprisingly free of headaches (18). Previous studies have focused on the prevalence of tumour headache, clinical characteristics of headache, tumour characteristics and the effect of surgery. The mechanism of headache due to pituitary tumours remains unclear, and the importance of tumour size and location is still not settled. Contradictory findings have been reported (28, 32-36). Most studies of headache in pituitary patients are done at surgical departments without population based referral, and the majority of patients referred to surgery harbour macroadenomas. This is not representative for pituitary tumours in the general population. Study designs vary from small prospective uncontrolled observational studies, larger retrospective case series of consecutive patients and single case studies. Small sample sizes, retrospective assessment of outcomes and nocebo/placebo effects associated with tumours and surgical removal may influence results. The association between tumour characteristics such as type, size or location of pituitary lesions and current headache in a dose-response-relationship (Bradford-Hill criteria of causality (37)) would be expected if there is a true biological causal relationship between the tumours and the headaches. However, established predictors associated with symptomatic

benefit or risk in possible candidates for surgery are so far lacking. There are no controlled studies comparing current headache symptoms among patients who have or have not undergone surgery for pituitary adenomas.

This study set out to investigate the relationship between pituitary adenomas and headache:

Primary aim

1. Is there an association between pituitary adenomas and headache?

Secondary aims

- 1) Is there an association between type, size or location of pituitary tumours and headache complaints (i.e. dose-response-relationship)?
- 2) Is there a difference in current headache symptoms among non-operated patients and operated patients with pituitary adenomas?

3 Materials and methods

3.1 Study design

The study is a case series with follow-up of patients diagnosed with pituitary adenoma. The study consists of cross-sectional data of current headaches from patient interviews, and retrospective data from patient interviews and medical records (38).

3.2 Study population

All patients at St. Olavs University Hospital, Trondheim, Norway, diagnosed with pituitary adenoma during the 10 year period from January 2003 through December 2013 were eligible for inclusion in the study. Patients under 18 years of age (n=6), patients suffering from severe dementia or psychiatric illness (n=21), patients unable to speak English or Norwegian (n=6), patients living abroad (n=4), and patients missing baseline MRIs due to being operated elsewhere (n=4) were excluded.

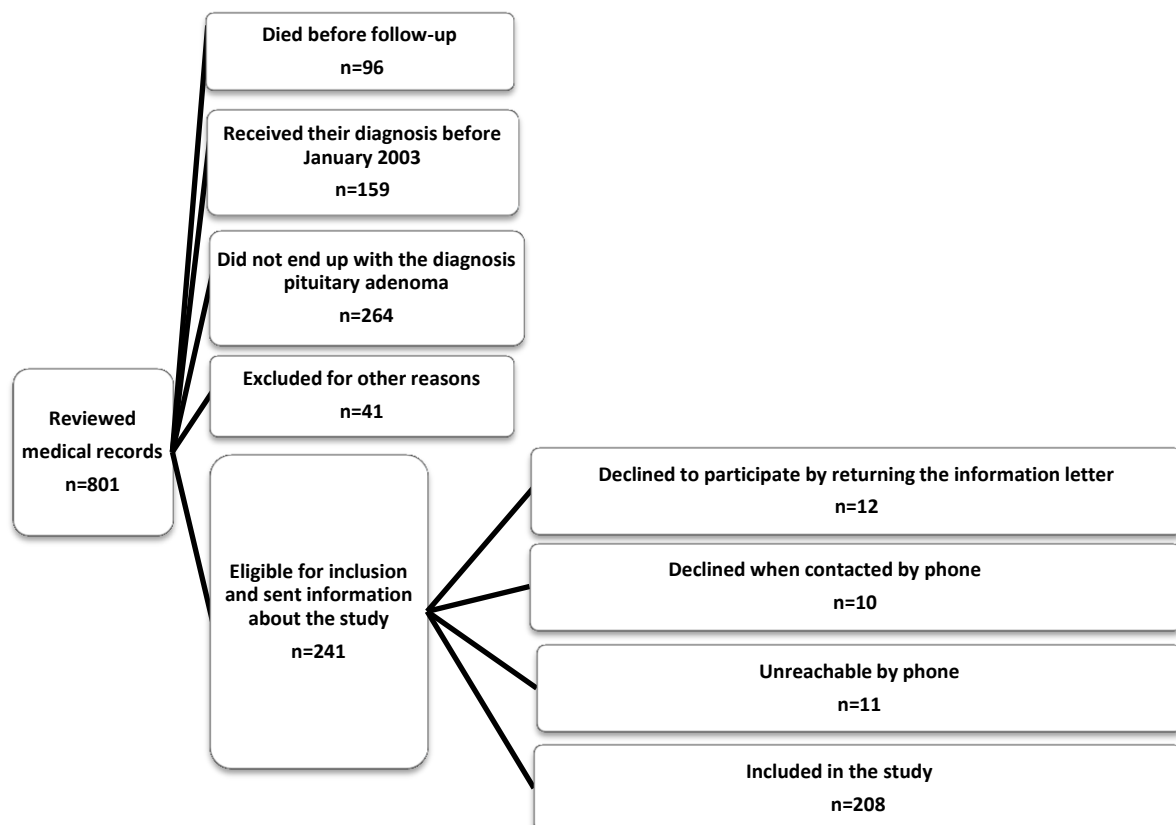


Figure 1 Flowchart

Medical records (n= 801) with the ICD-10 diagnostic codes and operation codes presented in Table 1, were screened to identify all patients referred to our hospital with pituitary adenomas

in the study period. The relevant diagnostic and procedure codes were decided in cooperation with an endocrinologist (SF).

Table 1 Diagnostic codes

| Code | Diagnosis description |
|-------------|--|
| D35.2 | Benign neoplasm of pituitary gland |
| D44.3 | Neoplasm of uncertain behaviour of pituitary gland |
| E22.0 | Acromegaly and pituitary gigantism |
| E22.1 | Hyperprolactinemia |
| E22.8 | Other hyperfunction of pituitary gland |
| E22.9 | Hyperfunction of pituitary gland, unspecified |
| E23.0 | Hypopituitarism |
| E23.7 | Disorder of pituitary gland, unspecified |
| E24.0 | Pituitary-dependent Cushing's disease |
| R90.0 | Abnormal findings in the central nervous system using imaging |
| AEE10 | Transsphenoidal extirpation or resection of an intracranial lesion |
| AEE00 | Transsphenoidal exploration |

3.3 Data collection

As seen in Figure 1, 241 patients were eligible for inclusion. All eligible patients were sent a letter dated March 2014 with information about the study and informing them that they would be contacted by phone (Appendix 1).

Patients who did not want to be contacted could decline by using a prepaid postage envelope enclosed in the information letter or by phone. Remaining patients were called up no sooner than 4 weeks after they received the information letter. If they currently did not have headache or never had, the interview lasted less than 5 minutes. If they suffered from headaches, the interview lasted approximately 15 minutes.

Information obtained from the patients' medical records and image data included variables concerning the treatment of the pituitary tumour, type of tumour, endocrine variables, MRI variables and headache (Appendix 2).

All interviews and reviews were conducted by an experienced research nurse (GBG). A consultant neurosurgeon (OS) reviewed all MRIs (Appendix 3). The interviews were finalized in August and the review of MRIs was done by October 2014. The expenses were covered by the Norwegian National Headache Centre.

Median time between the diagnostic MRI and the patient interview was 65 months (range 5 to 120 months). Median time from the last MRI and patient interview was 12 months (range 0 to 111 months).

3.4 Headache assessment

To be classified as headache sufferers at the time of diagnosis, headache had either to be specified in the medical records, or headache suffering the year preceding the diagnosis had to be stated by the patients in the interview. Acute headaches lasting less than a week, or related to other acute illnesses was not classified as headache. Current headache was defined according to the validated HUNT question: “Have you suffered from headaches during the last year?” (8, 9).

3.5 Hormone assessment

Hormone derangement treated with medication was included in the analysis. Types of tumours were divided into functional and non-functional adenoma. Functional adenoma was subdivided based on secretion of prolactin, growth hormone or ACTH.

3.6 Radiological assessment

The diagnostic and the most current MRIs were reviewed. The tumours were classified into four grades according to the modified Hardy’s grading system (39):

- < 10 mm in sella turcica (microadenoma).
- 0-20 mm, suprasellar extent within 10 mm of planum sphenoidale.
- 20-40 mm, suprasellar extent up to 30 mm, elevates or fills anterior third ventricle.
- 40 mm, extent far beyond sellar space with lateral or multiple expansions.

Tumours were also classified according to the largest diameter in the coronal plane (d_1), the diameter 90 degrees on the largest diameter of the coronal plane (d_2), and the largest diameter in the sagittal plane (d_3) (21). The volumes of the tumours were calculated as $\frac{\pi}{6} \cdot d_1 \cdot d_2 \cdot d_3$.

We assessed lifting of the diaphragma sella (Y/N), pressure on the visual nerve (no contact, contact, lifting), growth into sinus cavernosus (Y/N), expansion of sella turcica (destruction, Y/N) and growth through the floor into the sphenoidal sinus (Y/N).

3.7 Statistical analysis

Statistical analysis of the clinical data was performed using IBM SPSS Statistics 21 for Windows. Descriptive statistics were used to calculate prevalence and frequencies of the different variables of headache, hormones, types of tumours and measurements from MRIs. Categorical variables were compared using Chi-square test. Mann-Whitney U test was used to check for possible associations between tumour sizes and headache. A Chi-square goodness-of-fit was used to compare our population to the HUNT population. Prevalence of headache

was age- and sex-adjusted to the HUNT 3 population. Results were considered significant at a level of $p < 0.05$.

3.8 Ethics

The study was approved by the local Regional Committee for Medical and Health Research Ethics (REC). Answering the questions on the phone served as an affirmation of informed consent.

4 Results

4.1 Pituitary adenomas and headache

Of 241 eligible patients, 208 (86.3%) agreed to participate in the study. 96 (46 %) were men and 112 (54 %) women. Mean age was 59 (\pm 14) years in males and 49 (\pm 15) years in females. Table 2 lists the indications leading to the diagnostic MRI.

Table 2 Main symptoms that lead to the diagnostic MRI

| Symptom | No. of patients (%) |
|--|---------------------|
| Headache | 25 (12) |
| Visual problems | 31 (15) |
| Hormone related # ¹ | 39 (19) |
| Several unspecific general symptoms # ² | 50 (24) |
| Incidental finding, neuroimaging for other conditions # ³ | 57 (27) |
| Acute bleeding in tumour | 6 (3) |
| Total | 208 (100) |

#¹ menstrual cycle, lactation, libido, impotence

#² pain, fatigue, exhausted, dizziness, unwell, sleep problems, weight increase, body change, acne, thirst, nausea

#³ stroke/TIA, fall, fractures, syncope, eye/ear/neck/back problems, abnormal blood test

Based on a synthesis of the patients' recollection in the interviews and reviews of medical records, 108 (52%) of the patients were classified as headache sufferers the year before they were diagnosed with pituitary tumour. However, 7 of these presented with acute headaches within days before they were diagnosed. In 6 of these 7 patients, a bleeding/apoplexy was seen on the initial MRI, making pituitary apoplexy a likely cause of the acute headache. In one patient a sinus infection was the likely cause of the acute headache.

Table 3 Prevalence of headaches before and after being diagnosed with pituitary tumours

| | All, n (%) | Male, n (%) | Female, n (%) |
|--|------------------|-----------------|------------------|
| According to interviews | 85 (41) | 38 (40) | 47 (42) |
| From medical record | 90 (43) | 46 (48) | 44 (39) |
| Both | 67 (32) | 31 (32) | 36 (32) |
| Total prevalence at diagnosis | 108 (52) | 53 (55) | 55 (49) |
| Acute headaches at diagnosis | 7 (3) | 5 (5) | 2 (2) |
| Non-acute headaches at diagnosis | 101 (49) | 48 (50) | 53 (47) |
| Headache the last year (at follow-up) | 54 (26) | 21 (22) | 33 (30) |
| New headache after treatment | 11 (5) | 4 (4) | 7 (6) |
| Total | 208 (100) | 96 (100) | 112 (100) |

A family history of headache was significantly more common in headache sufferers (51%) than in non-headache patients (35%) (p=0.020).

4.2 *Prevalence of non-acute headache compared to the general population*

Table 3 provides the non-adjusted prevalence data of non-acute headache at diagnosis and at follow-up.

The age and sex-adjusted prevalence of headache before being diagnosed with pituitary adenomas was 48%; 36% in men and 58% in women. The age and sex-adjusted prevalence of headache is significantly higher at the time of diagnosis (48%) compared to the general population (37%) as seen in the HUNT 3 study ($p < 0.001$) (5, 6).

The age and sex-adjusted prevalence of headache the last year was 21%; 13% in men and 28% in women, which is significant lower ($p < 0.001$) than in the general population in the HUNT 3 study (37%) (6).

4.3 *Type, size or location of pituitary tumour and headache*

Table 4 Type of tumour and headaches

| | Headache at diagnosis, n/N (%) | Current headache, n/N (%) |
|------------------------|--------------------------------|---------------------------|
| NFA | 53/106 (50) | 27/106 (26) |
| FA | 48/102 (47) | 27/102 (27) |
| GH-producing adenoma | 16/26 (62) | 10/26 (38) |
| ACTH-secreting adenoma | 9/21 (43) | 4/21 (19) |
| Prolactinoma | 23/55 (42) | 13/55 (24) |
| Total | 101/208 (49) | 54/208 (26) |

As seen in Table 4, there were no apparent overall differences in headache prevalence at diagnosis or at follow-up between patients with functional and non-functional adenomas ($p = 0.671$ and $p = 0.870$).

Table 5 Headache and hormone deficiency

| | Headache at diagnosis, n/N (%) | Current headache, n/N (%) |
|--------------------------------|--------------------------------|---------------------------|
| Hormone deficiencies | 34/69 (49%) | 27/82 (33%) |
| No hormone deficiencies | 67/139 (48%) | 27/126 (21%) |

Headache was not significantly more common among patients with hormone deficiencies at diagnosis ($p = 0.884$) or at follow-up ($p = 0.065$), as seen in Table 5. Similarly, current headache was not more common in patients with hormone overproduction (29% vs 25%, $p = 0.518$). Secondary hyperprolactinemia due to pituitary stalk compression seen in 39 patients was not associated with headache before diagnosis ($p = 0.982$) or at follow-up ($p = 0.389$).

Table 6 Headache in MRI measured characteristics

| | n/N (%) | | | | | |
|--|--------------------------|--|----------|---------------------|--|----------|
| | Headache(n) at diagnosis | Headache(n) in controls with other MRI characteristics | p-value* | Current headache(n) | Headache(n) in controls with other MRI characteristics | p-value* |
| < 10 mm in sella turcica | 26/61 (43) | 74/145 (51) | 0.511 | 15/52 (29) | 36/142 (25) | 0.710 |
| 0-20 mm, suprasellar extent within 10 mm of planum sphenoidale | 33/64 (52) | 67/142 (47) | 0.733 | 7/39 (18) | 44/15 (28) | 0.299 |
| 20-40 mm, suprasellar extent up to 30 mm, elevates or fills anterior third ventricle | 18/44 (41) | 82/162 (51) | 0.493 | 4/7 (57) | 47/187 (25) | 0.194 |
| 40 mm, extent far beyond sellar space with lateral or multiple expansions | 23/37 (62) | 77/169 (46) | 0.298 | 4/23 (17) | 47/171 (28) | 0.415 |
| Lifting of the sella diaphragm | 75/145 (52) | 26/62 (42) | 0.443 | 11/47 (23) | 40/147 (27) | 0.691 |
| Pressure on the visual nerve | 28/57 (49) | 73/150 (49) | 0.973 | 2/8 (25) | 49/186 (26) | 0.948 |
| Growth into sinus cavernosus | 26/54 (48) | 75/153 (49) | 0.948 | 9/41 (22) | 42/153 (28) | 0.582 |
| Expansion of sella turcica | 54/99 (55) | 47/108 (44) | 0.353 | 7/43 (16) | 44/151 (29) | 0.183 |
| Growth through the floor into sphenoidal sinus | 21/35 (60) | 80/172 (47) | 0.407 | 4/15 (27) | 47/179 (26) | 0.979 |
| No tumour-remnant | NA | NA | NA | 21/75 (28) | 30/119 (25) | 0.743 |
| Total number of available MRIs | 101/207 [#] | | | 51/194 [†] | | |

NA: Not applicable

*Chi-square test

[#]MRI characteristics at diagnosis were missing in 2 patients.

[†]Total number of available MRI images at follow up were 194, 51 headache sufferers.

There appears to be no clear dose-response associations between headache and assessed MRI characteristics as seen in Table 6.

There were no differences in largest tumour diameters or calculated tumour volumes for patients with or without headaches before being diagnosed (median [range] diameter 17.0 [0-55] mm vs 16.5 [0-47] mm, Mann-Whitney U test p=0.329 and volume 1.62 [0-37.32] ml vs 1.71 [0-28.82] ml, p=0.310).

Nor were there differences in the largest tumour diameters or calculated tumour volumes from the most recent MRIs in patients with or without current headache (median [range] diameter

6.0 [0-29] mm vs 7.0 [0-45] mm, Mann-Whitney U test p=0.277 and volume 0.07 [0-6.56] ml vs 0.08 [0-12.20] ml, p=0.383).

4.4 Does pituitary surgery reduce headache?

Table 7 Headache change in operated and non-operated patients

| | n/N (%) | | | | Total n=208 |
|--|--|---|---|--|------------------------|
| | Operated patients n=127 #¹ | Non-operated patients n=81 | Medication only n=55 #² | No treatment n=26 #³ | |
| Non-acute headache at diagnosis | 68/127 (54) | 33/81 (41) | 23/55 (42) | 10/26 (38) | 101/208 (49) |
| Cured: Non-acute headache at diagnosis and no headache the last year | 40/68 (59) | 18/33 (55) | 13/23 (57) | 5/10 (50) | 58/101 (57) |
| Improved: Non-acute headache at diagnosis and improvement in experienced headache the last year | 16/68 (24) | 4/33 (12) | 4/23 (17) | 0 (0) | 20/101 (20) |
| Unchanged: Non-acute headache at diagnosis and headache the last year | 8/68 (12) | 10/33 (30) | 5/23 (22) | 5/10 (50) | 18/101 (18) |
| Worse: Non-acute headache at diagnosis and worsening in experienced headache the last year # ⁴ | 4/68 (6) | 1/33 (3) | 1/23 (4) | 0 (0) | 5/101 (5) |
| New headache: No headache at diagnosis, but headache at follow-up | 5/59 (8) | 6/48 (13) | 4/32 (13) | 2/16 (13) | 11/107(10) |

#¹: 79 NFA, 24 GH excess, 21 ACTH, 3 prolactinomas

#²: 50 prolactinomas, 1 excess GH, 4 NFA (secondary hyperprolactinemia initially mistaken for prolactinomas)

#³: 23 NFA, 1 low-degree excess GH, 2 prolactinomas

#⁴: 1 prolactinoma (medication only), 2 NFA, 1 excess GH, 1 excess ACTH

Table 7 shows that out of 101 patients with headache at diagnosis, 58 (57%) are no longer suffering from headaches, and 20 (20%) report significant improvement at follow up.

In total 78/101 (77%) report resolved or improved headaches. Improvement or cure of headaches was not statistically significantly more common among operated patients than among non-operated patients, 56/68 (82%) versus 22/33 (67%) (p=0.521).

Four patients (6% of operated) experienced worsening of their previous headaches after surgery. Eleven (10%) patients with no headache at diagnosis suffer from headaches at follow up.

Table 8 Headache in operated and non-operated patients versus HUNT 3 population

| | n (%) | | | |
|---|------------------------------------|---------------------------------------|------------------------|---------------------------|
| | Operated patients n=127 | Non-operated patients n=81 | Total n=208 | HUNT 3 n=39690 |
| Headache the last year | 33 (26) | 21 (26) | 54 (26) | 14220 (37) |
| Migraine the last year (self-considered migraine) | 4 (3) | 4 (5) | 8 (4) | 3059 (8) |
| Migraine according to 2010 diagnostic (restrictive) criteria #¹ | 4 (3) | 10 (12) | 14 (7) | 4404 (12) |
| Non-migrainous headache the last year | 29 (23) | 18 (22) | 47 (23) | 9329 (24) |
| Chronic headache >14 days per month | 12 (9) | 8 (10) | 20 (10) | 973 (3) |

#¹ ICHD-II 2004 (7) except duration of headache, more closely described in reference (6, 9).

In Table 8, the current prevalence of headache subtypes among operated and non-operated patients are presented together with data from the general population (6).

There is no significant difference between operated and non-operated patients in terms of headaches, except when assessing headache symptoms according to the restrictive 2010 ICHD-II diagnostic criteria. The prevalence of migraine among non-operated patients is similar to in the HUNT 3 population (12% vs. 12%), but operated patients report significantly less seldom migraine than non-operated patients (3% vs. 12%, $p=0.017$).

The prevalence of current chronic headache is also significantly higher in patients with pituitary tumours compared to the general population in the HUNT 3 study (10% vs. 3%, $p<0.001$) (6).

5 Discussion

5.1 *Main findings*

Approximately 1 in 4 patients previously diagnosed with pituitary adenomas report that they suffered from headaches the last year at follow-up. Curiously, this is lower than found in the age- and sex-adjusted general population (6). Since residual tumours are common after treatment and our cohort also includes untreated patients, this finding may suggest that there is no apparent biological association between headache and pituitary tumours. Still, the prevalence of current chronic headache is significantly higher both in operated (9%) and non-operated (10%) patients compared to the general population (3%). Also, operated patients more seldom report migraine according to the restrictive 2010 ICHD-II diagnostic criteria (9). Although retrospective assessment of headaches from medical records and interviews are prone to bias, headache prevalence was significantly higher than in the general population at diagnosis. Approximately 3 in 4 patients with headaches reported relief or significant improvement of their headache at follow up, included a 50% “cure-rate” even in untreated patients. The lack of an apparent “dose-response” association between endocrine or MRI characteristics and headache among patients with pituitary tumours suggests that the great symptom relief after treatment may not necessarily represent a cause-effect relationship. A significant placebo effect from treatment cannot be ruled out and improvements may also be due to regression to the mean, over time since patients often seek medical advice, are diagnosed and treated in periods with high symptom burdens. A family history of headache was significantly associated with headache among patients with pituitary adenomas, further suggesting that other factors than the tumour may be important in patients with headache and pituitary tumours. Except for family history of headache, we were unable to identify any clinical, endocrinological or radiological factors associated with headache in patients with pituitary tumours, both prior to and after treatment.

5.2 *Clinical interpretation*

Previous studies have used non-validated headache parameters so the true prevalence of headache at diagnosis is still uncertain and unselected population based series are lacking. A recent systematic review claims that headache is very common in pituitary disease, and is present in more than a third of all patients with pituitary adenomas (28). A retrospective study in 4050 patients operated for pituitary adenomas reported that 69% experienced headaches before surgery (39).

Headache may be a common cause for undergoing diagnostic cerebral MRIs that may lead to the incidental discovery of pituitary adenomas (40). The availability of MRI is exceptionally high in Norway and the number of benign extra-axial brain tumours due to incidental findings are therefore rising (41). This might have affected the case-mix in our study. One could also speculate if patients that are diagnosed with pituitary tumours expect that intracranial tumours could cause headaches and are particularly sensitive to cranial symptoms that would otherwise be ignored. As shown in the result section few of our patients had headache as their main symptom leading to the diagnostic MRI. Similar numbers (women 11 %, men 16%) have previously been reported (42). In contrast, a recent retrospective study found that 24% had headache as their chief complaint before surgery (43).

Current headache was assessed using validated questions from the population based HUNT studies (8, 9). Prevalence data was age and sex-adjusted to the HUNT 3 population. For the genders combined the headache prevalence was significantly lower (21%) compared to the general population (37%) (6). Although we utilized the same study questions as in the population based HUNT study (5, 6) for assessing current complains, the retrospectively assessed headache prevalence at diagnosis might be influenced by the quality of recall (3). At times, answers were inconsistent, and in conflict with documentation from medical records. We therefore used a synthesis of recalled data and data from medical records for assessing the headache prevalence at diagnosis. Acute headaches were excluded since pituitary apoplexy is a known cause of headache (26-28).

Non-functional adenomas (51%) were dominating in our study population and there were relatively few prolactinomas (26%). This high proportion of non-functional adenomas is seen in most studies of headache in patients with pituitary tumours (15, 35, 36). Still, this differs from large population based studies (11, 13, 16) where prolactinomas are the most common adenomas. Levy et al. stated that headache can be dramatically improved or worsened by endocrine treatment, and in the absence of any measurable change in pituitary size, suggests that pituitary associated headache may be a biochemical neuroendocrine problem rather than a structural one (32). In our material hormone deficiency is based on the interpretation of laboratory tests performed by the treating clinician. We found no evidence that type of tumour, hormone production or hormone deficiency could predict headache either before the diagnosis or at follow-up.

In our study we found that a family history of headache was significantly associated with headaches among patients with pituitary adenomas. These results have been supported by other studies. Levy et al. found a strong association with family history (>5 years) of

headache and pituitary-associated-headache (32). An association between pituitary tumour and a family history of headache has also been found by Schankin et al. (36), but not Gondim et al. (33).

It has also been suggested that pituitary tumours may lower the threshold for migraines and that phenotypic family headaches might be important (15). Headache in patients with pituitary adenomas have many of the characteristics of primary headaches. Levy et al. investigated and classified 84 patients according to ICHD-II criteria finding that 76% fulfilled the criteria of migraine (34). When assessing the headache symptoms in our data according to the validated restrictive migraine criteria (9), the non-operated patients had a prevalence of migraine (restrictive) of 12%, identical to the HUNT 3 study (6), while only 3% of the patients who underwent surgery had a headache that meets the criteria of migraine.

The non-surgery group consisted of mainly prolactinomas that are more prevalent in women and often diagnosed at a younger age. Migraine is more prevalent in women (15%) than men (7%), and the prevalence drops markedly after the age of 60 (6). At follow-up, all the participants have become older (mean age 59 years in men and 49 in women), and the headache prevalence is expected to fall due to aging (44, 45).

We found no association between tumour characteristics and headache in our data. A recent retrospective review of 1015 patients with sellar lesions (66% adenomas) found that patients with gross total resection (GTR) achieved postoperative headache improvement, in line with the hypothesis that the underlying cause of headache is mass effect (43). In contrast to this, 61% (119) of the patients in our study have tumour-remnants at follow-up, but tumour remnant was not associated with headache. A recent study of clinical characteristic of pain found headaches equally frequent in microadenomas and macroadenomas (46).

We did not find any association between assessed MRI variables and headaches, neither before surgery nor at follow-up. This includes invasion of the cavernous sinus, lifting of the optic nerves or chiasm or tumour size. The mechanisms of headache in pituitary tumours therefore remain unclear.

Increased intra sellar pressure has also been postulated as cause of headache in pituitary adenoma (47). Abe et al. reported that none of the patients with pituitary adenoma and headache had symptoms of elevated intracranial pressure (35). Early studies found that headache in patients with intracranial tumours is related to tumour size and dural stretch (48, 49), but these findings have been questioned in later studies (32). Gondim et al. found an association between headache and invasion of the cavernous sinus and that an important factor in the genesis of the headache is the speed of tumour growth and the ability of the sellar

walls to modulate this growth (33). These results were later challenged by Schankin et al. who suggested that the systemic endocrine processes or cavernous sinus invasion may be of less importance and reported that headache was associated with increased intrasellar pressure caused by highly proliferative tumour tissue (36). Tumours might act as triggers in patients predisposed to primary headaches and local tumour effects or lifestyle factors could be predisposing mechanisms (36). No prospective clinical study has demonstrated a correlation between tumour headache and endocrine function of the adenoma (36).

The prevalence of chronic headache was higher in our data than in the general population. Still, chronic headache was not associated with type of treatment, MR variables, hormones or a family history of headache. Previous studies have not reported number of days of headaches. Chronic headache more than 14 days per month the past months might be easier to recall than fewer days. In our study, the current prevalence of total headache, self-considered migraine, non-migrainous headache and chronic headache does not differ between operated and non-operated patients.

More than half of the patients in this study experienced a resolution of their headaches. Improvement of headache after treatment was not significantly more prevalent in operated patients. The subjective perceived improvement assessed retrospectively and not documented in a headache diary. Improvement may be due to psychosocial factors, such as the expectation of therapeutic benefit, biases, and co-interventions (50). In chronic disorders such as headache, the natural cause of a disease, spontaneous improvement and fluctuation of symptoms are special forms of *regression to the mean* (the tendency of extreme values to move closer to the average on repeated measurement) (51, 52).

Although improvement in headache following pituitary treatment could imply a causal link between the tumour and the presence of headache, it is difficult to control for possible confounding variables or the natural history (34). Several other studies have reported improvement in headaches after treatment but acknowledge possible contributing factors, including the long time before follow up (34-36). Fleseriu et al. have published remarkable results in a retrospective study of 41 patients with microadenomas and severe treatment refractory headaches who underwent transsphenoidal surgery. 85% reported relief of headache symptoms after surgery. Still, information about headache before surgery and tumour characteristics was lacking, and the authors acknowledge that a significant placebo effect was not unlikely (15).

The evidence of an association between pituitary adenomas and headache remains weak and headache alone is still a controversial indication for pituitary surgery (1). Studies that report

contradictive findings may have been hampered by relatively small number of patients making it difficult to draw conclusions, not at least from subgroups (28).

5.3 Strengths and weaknesses

In this study a combined method of retrospective review of hospital medical records and follow-up patient interviews was chosen in order to assess the relevant hospital-based population within a manageable timeframe, while minimizing selection and information bias. This is the largest study examining the association between pituitary adenoma and headache to date. The size of the study, the validated questionnaires, the participation rate and unselected study population increases generalizability of findings. Furthermore, the study was done in patients with similar cultural background as the population based study used for controls (HUNT), and within the same hospital catchment region. A large number of diagnostic codes were assessed to detect the cases.

The study used several sources of information, such as patient interviews, MRI and medical records to consolidate and enhance the quality of the data.

The calculated age and sex-adjusted prevalence enhances the external validity of the data in comparison to the general population. Furthermore, the 1-year prevalence of “restrictive” migraine was calculated using the validated questionnaire employed in HUNT 3 (6, 9).

All the interviews were done by the same interviewer and the images were interpreted by the same neurosurgeon (blinded for whether the patient had headaches) which further increases rater reliability of the data.

The retrospective gathering of information is challenged by missing data and danger of misinterpretations. Patients are inconsistent when reporting past headaches due to recall bias and the self-improvement effect. Ninety-six patients died before inclusion, and the few patients who declined to participate increase the risk of a non-responder bias. Some patients with small pituitary tumours with easily treatable hormone disturbances, and without indication for surgery, had been followed up at their local hospital or general practitioners and may therefore be underrepresented. This may explain the lack of prolactinomas in the population and the relatively few untreated patients.

Direct comparison of hormone laboratory values was not possible due to use of different test methods and time points over the years. Depending on the course of the illness the latest MR images was taken at different time points (median 12 months before the interviews). Multiple statistically significant testing in small subgroups increases the risk of false positive p-values.

5.4 *Implications for future research*

A large prospective study with standardized endocrinological and surgical treatment with accurate clinical subtyping of headaches according to ICHD-III at diagnosis, perhaps with a special emphasis of chronic headaches may be the next step in identifying which patient who may benefit of surgery in terms of headache relief.

6 Conclusion

Many patients retrospectively reported relief of headache complaints after surgery. Compared to the general population the current prevalence of headaches among patients harbouring both treated and untreated pituitary adenomas is low. A family history of headache was significantly more common in headache sufferers but due to the lack of identified modifiable variables associated with headache we suggest that headache alone as a sole indication for treatment remains questionable.

7 References

1. Freda PU, Beckers AM, Katznelson L, Molitch ME, Montori VM, Post KD, et al. Pituitary incidentaloma: an endocrine society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*. 2011;96(4):894-904.
2. Headache Classification Committee of the International Headache S. The International Classification of Headache Disorders, 3rd edition (beta version). *Cephalalgia : an international journal of headache*. 2013;33(9):629-808.
3. Stovner LJ. Headache epidemiology: how and why? *The journal of headache and pain*. 2006;7(3):141-4.
4. Scheel HH. Statistisk årbok 2013. Modig I, editor. Oslo: statistisk sentralbyrå; 2013.
5. Hagen K, Zwart JA, Vatten L, Stovner LJ, Bovim G. Prevalence of migraine and non-migrainous headache--head-HUNT, a large population-based study. *Cephalalgia : an international journal of headache*. 2000;20(10):900-6.
6. Linde M, Stovner LJ, Zwart JA, Hagen K. Time trends in the prevalence of headache disorders. The Nord-Trondelag Health Studies (HUNT 2 and HUNT 3). *Cephalalgia : an international journal of headache*. 2011;31(5):585-96.
7. Olesen J, Steiner TJ. The International classification of headache disorders, 2nd edn (ICDH-II). *Journal of neurology, neurosurgery, and psychiatry*. 2004;75(6):808-11.
8. Hagen K, Zwart JA, Vatten L, Stovner LJ, Bovim G. Head-HUNT: validity and reliability of a headache questionnaire in a large population-based study in Norway. *Cephalalgia : an international journal of headache*. 2000;20(4):244-51.
9. Hagen K, Zwart JA, Aamodt AH, Nilsen KB, Brathen G, Helde G, et al. The validity of questionnaire-based diagnoses: the third Nord-Trondelag Health Study 2006-2008. *The journal of headache and pain*. 2010;11(1):67-73.
10. Laws ER, Sheehan JP. *Sellar and Parasellar Tumors: Diagnosis, Treatments, and Outcomes*. New York : Stuttgart: Thieme; 2012.
11. Ezzat S, Asa SL, Couldwell WT, Barr CE, Dodge WE, Vance ML, et al. The prevalence of pituitary adenomas: a systematic review. *Cancer*. 2004;101(3):613-9.
12. Kopczak A, Renner U, Stalla GK. Advances in understanding pituitary tumors. *F1000prime reports*. 2014;6:5.
13. Daly AF, Rixhon M, Adam C, Dempegioti A, Tichomirowa MA, Beckers A. High prevalence of pituitary adenomas: a cross-sectional study in the province of Liege, Belgium. *The Journal of clinical endocrinology and metabolism*. 2006;91(12):4769-75.
14. Fernandez-Balsells MM, Murad MH, Barwise A, Gallegos-Orozco JF, Paul A, Lane MA, et al. Natural history of nonfunctioning pituitary adenomas and incidentalomas: a systematic review and metaanalysis. *The Journal of clinical endocrinology and metabolism*. 2011;96(4):905-12.
15. Fleseriu M, Yedinak C, Campbell C, Delashaw JB. Significant headache improvement after transsphenoidal surgery in patients with small sellar lesions. *Journal of neurosurgery*. 2009;110(2):354-8.
16. Fernandez A, Karavitaki N, Wass JA. Prevalence of pituitary adenomas: a community-based, cross-sectional study in Banbury (Oxfordshire, UK). *Clinical endocrinology*. 2010;72(3):377-82.

17. Gittleman H, Ostrom QT, Farah PD, Ondracek A, Chen Y, Wolinsky Y, et al. Descriptive epidemiology of pituitary tumors in the United States, 2004-2009. *Journal of neurosurgery*. 2014;121(3):527-35.
18. Powell M, Lightman SL, Laws ER. *Management of pituitary tumors : the clinician's practical guide*. 2nd ed. Totowa, N.J.: Humana Press; 2003.
19. Rogers A, Karavitaki N, Wass JA. Diagnosis and management of prolactinomas and non-functioning pituitary adenomas. *BMJ (Clinical research ed)*. 2014;349:g5390.
20. Neggers SJCMM, van der Lely AJ. Medical approach to pituitary tumors. In: Eric Fliers MK, Johannes AR, editors. *Handbook of clinical neurology*: Elsevier; 2014. p. 303-16.
21. Buchfelder M, Schlaffer S. Imaging of pituitary pathology. In: Eric Fliers MK, Johannes AR, editors. *Handbook of clinical neurology*: Elsevier; 2014. p. 151-66.
22. Samarasinghe S, Emanuele MA, Mazhari A. Neurology of the pituitary. In: José B, José MF, editors. *Handbook of clinical neurology*: Elsevier; 2014. p. 685-701.
23. Carlsen SM, Svartberg J, Schreiner T, Aanderud S, Johannesen O, Skeie S, et al. Six-month preoperative octreotide treatment in unselected, de novo patients with acromegaly: effect on biochemistry, tumour volume, and postoperative cure. *Clinical endocrinology*. 2011;74(6):736-43.
24. Pita-Gutierrez F, Pertega-Diaz S, Pita-Fernandez S, Pena L, Lugo G, Sangiao-Alvarellos S, et al. Place of preoperative treatment of acromegaly with somatostatin analog on surgical outcome: a systematic review and meta-analysis. *PloS one*. 2013;8(4):e61523.
25. Nunes VS, Correa JM, Puga ME, Silva EM, Boguszewski CL. Preoperative somatostatin analogues versus direct transsphenoidal surgery for newly-diagnosed acromegaly patients: a systematic review and meta-analysis using the GRADE system. *Pituitary*. 2014:Epub ahead of print.
26. Nawar RN, AbdelMannan D, Selman WR, Arafah BM. Pituitary tumor apoplexy: a review. *Journal of intensive care medicine*. 2008;23(2):75-90.
27. Capatina C, Inder W, Karavitaki N, Wass JA. Management of endocrine disease: Pituitary tumour apoplexy. *European journal of endocrinology / European Federation of Endocrine Societies*. 2015;172(5):R179-R90.
28. Kreitschmann-Andermahr I, Siegel S, Weber Carneiro R, Maubach JM, Harbeck B, Brabant G. Headache and pituitary disease: a systematic review. *Clinical endocrinology*. 2013;79(6):760-9.
29. Solari D, Cavallo LM, Cappabianca P. Surgical approach to pituitary tumors. In: Eric Fliers MK, Johannes AR, editors. *Handbook of clinical neurology*: Elsevier; 2014. p. 291-301.
30. Solheim O, Jakola AS, Gulati S, Johannesen TB. Incidence and causes of perioperative mortality after primary surgery for intracranial tumors: a national, population-based study. *Journal of neurosurgery*. 2012;116(4):825-34.
31. Katznelson L, Laws ER, Jr., Melmed S, Molitch ME, Murad MH, Utz A, et al. Acromegaly: an endocrine society clinical practice guideline. *The Journal of clinical endocrinology and metabolism*. 2014;99(11):3933-51.
32. Levy MJ, Jager HR, Powell M, Matharu MS, Meeran K, Goadsby PJ. Pituitary volume and headache: size is not everything. *Archives of neurology*. 2004;61(5):721-5.

33. Gondim JA, de Almeida JP, de Albuquerque LA, Schops M, Gomes E, Ferraz T. Headache associated with pituitary tumors. *The journal of headache and pain*. 2009;10(1):15-20.
34. Levy MJ, Matharu MS, Meeran K, Powell M, Goadsby PJ. The clinical characteristics of headache in patients with pituitary tumours. *Brain*. 2005;128:1921-30.
35. Abe T, Matsumoto K, Kuwazawa J, Toyoda I, Sasaki K. Headache associated with pituitary adenomas. *Headache*. 1998;38(10):782-6.
36. Schankin CJ, Reifferscheid AK, Krumbholz M, Linn J, Rachinger W, Langer S, et al. Headache in patients with pituitary adenoma: clinical and paraclinical findings. *Cephalalgia : an international journal of headache*. 2012;32(16):1198-207.
37. Hill AB. The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*. 1965;58(5):295-300.
38. Portney LG, Watkins MP. *Foundations of clinical research : applications to practice*. 3rd ed. Upper Saddle River, N.J.: Pearson/Prentice Hall; 2009.
39. Shou XF, Li SQ, Wang YF, Zhao Y, Jia PF, Zhou LF. Treatment of pituitary adenomas with a transsphenoidal approach. *Neurosurgery*. 2005;56(2):249-56.
40. Levy MJ. The association of pituitary tumors and headache. *Current neurology and neuroscience reports*. 2011;11(2):164-70.
41. Solheim O, Torsteinsen M, Johannesen TB, Jakola AS. Effects of cerebral magnetic resonance imaging in outpatients on observed incidence of intracranial tumors and patient survival: a national observational study. *Journal of neurosurgery*. 2014;120(4):827-32.
42. Stoffel-Wagner B, Stoger P, Klingmuller D. [Initial symptoms and anamnestic time in 517 patients with pituitary adenoma]. *Deutsche medizinische Wochenschrift*. 1997;122(8):213-9.
43. Jahangiri A, Wagner JR, Chin AT, Han SW, Tran MT, Miller LM, et al. Incidence of headache as a presenting complaint in over 1000 patients with sellar lesions and factors predicting postoperative improvement. *Clinical neurology and neurosurgery*. 2015;132C:16-20.
44. Rasmussen BK, Jensen R, Schroll M, Olesen J. Epidemiology of headache in a general population—A prevalence study. *Journal of clinical epidemiology*. 1991;44(11):1147-57.
45. Bigal ME, Liberman JN, Lipton RB. Age-dependent prevalence and clinical features of migraine. *Neurology*. 2006;67(2):246-51.
46. Dimopoulou C, Athanasoulia AP, Hanisch E, Held S, Sprenger T, Toelle TR, et al. Clinical characteristics of pain in patients with pituitary adenomas. *European journal of endocrinology / European Federation of Endocrine Societies*. 2014;171(5):581-91.
47. Arafah BM, Prunty D, Ybarra J, Hlavín ML, Selman WR. The dominant role of increased intrasellar pressure in the pathogenesis of hypopituitarism, hyperprolactinemia, and headaches in patients with pituitary adenomas. *The Journal of clinical endocrinology and metabolism*. 2000;85(5):1789-93.
48. Forsyth PA, Posner JB. Headaches in patients with brain tumors: a study of 111 patients. *Neurology*. 1993;43(9):1678-83.
49. Suwanwela N, Phanthumchinda K, Kaorophum S. Headache in brain tumor: a cross-sectional study. *Headache*. 1994;34(7):435-8.
50. Benedetti F. *Placebo effects*. 2nd ed: Oxford University Press; 2014.

51. Kienle GS, Kiene H. The powerful placebo effect: fact or fiction? *Journal of clinical epidemiology*. 1997;50(12):1311-8.
52. McDonald CJ, Mazzuca SA, McCabe GP, Jr. How much of the placebo 'effect' is really statistical regression? *Statistics in medicine*. 1983;2(4):417-27.

8 Appendix

8.1 *Appendix 1 Patient information/consent*

8.2 *Appendix 2 Questionnaire*

8.3 *Appendix 3 MR variables registration schema*

Forespørsel om deltakelse i forskningsprosjektet

Hypofysesvulst og hodepine

Er det en sammenheng og hjelper kirurgi (operasjon)?

Bakgrunn og hensikt

Dette er et spørsmål til deg om å delta i en forskningsstudie for å finne forekomsten av hodepine blant pasienter diagnostisert med hypofyse-svulst ved St Olavs hospital, og finne ut om kirurgi(operasjon) reduserer hodepineplager.

For å finne ut hvor mange som plages med hodepine ønsker vi et kort telefonintervju med alle, enten de har opplevd hodepine eller ikke.

Hensikten er å finne hvor mange som plagdes med hodepine før de fikk diagnosen og om hodepinen har endret seg i tiden etterpå. Vi ønsker på denne måten å undersøke om det er forskjell i hodepineplager mellom de som blir operert og de som ikke blir operert. Vi er ute etter kunnskap om hypofysesvulster kan gi hodepine og om plagene påvirkes av kirurgisk behandling.

Hva innebærer samtykke i å delta i studien?

Du vil bli kontaktet en gang på telefon og spurt enkle spørsmål om hodepineplager.

Med din tillatelse vil forskerne ansatt ved St. Olavs hospital gå inn i din pasientjournal for å hente ut informasjon om hypofysesvulsten din, behandlingen du har fått for svulsten og studere MR bildene som ble tatt av hypofysen din. Ingen andre opplysninger vil bli hentet fra din sykejournal. Dersom du ikke har hodepine vil intervjuet være over på 5 minutter, og om du har hodepine tar det ca. 15 minutter.

Om du ikke ønsker å bli kontaktet kan du returnere dette brevet i den ferdig frankerte returkonvolutten innen 4 uker. Når vi ringer deg får du nok en anledning til å reservere deg mot å delta.

Om du ønsker å være med i studien og svarer på spørsmålene i telefonintervjuet, regner vi det som et samtykke til å delta.

Mulige fordeler og ulemper

Ulempene for deg er at du ved samtykke til og delta må svare på noen spørsmål på telefonen, noe som tar 5-15 minutter. Kunnskapen fra denne studien kan potensielt påvirke behandlingen av fremtidige pasienter med hypofysesvulst og hodepine.

Hva skjer med informasjonen om deg?

Informasjonen som registreres om deg skal kun brukes slik som beskrevet i hensikten med studien. Alle opplysningene og prøvene vil bli behandlet uten navn og fødselsnummer eller andre direkte gjenkjennerende opplysninger. En kode knytter deg til dine opplysninger gjennom en navneliste. Det er kun autorisert personell knyttet til prosjektet (de tre nedenfor) som har adgang til navnelisten og som kan finne tilbake til deg. Studien skal være ferdig våren 2015, og informasjonen vil oppbevares i 5 år før informasjonen slettes. Det vil ikke være mulig å identifisere deg i resultatene av studien når disse publiseres.

Frivillig deltakelse

Det er frivillig å delta i studien. Du kan når som helst og uten å oppgi noen grunn trekke ditt samtykke til å delta i studien. Dette vil ikke få konsekvenser for din videre behandling. Dersom du ønsker å delta, svarer du på spørsmålene når vi ringer. Om du nå sier ja til å delta, kan du senere trekke tilbake ditt samtykke uten at det påvirker din øvrige behandling.

Dersom du senere ønsker å trekke deg eller har spørsmål til studien, kan du kontakte Gøril Bruvik Gravdahl ved Nasjonalt kompetansetjeneste for hodepine på telefon 75 57 51 47.

Med vennlig hilsen

Prosjektleder:

Erling Tronvik
PhD / Nevrolog
Avdeling for nevrologi og klinisk nevrofysiologi
Telefon: 72 57 52 00

Prosjektmedarbeidere:

Ole Solheim
PhD / Nevrokirurg
Nevrokirurgisk avdeling
Telefon: 72 57 52 00

Gøril Bruvik Gravdahl
Forskningssykepleier
Nasjonal kompetansetjeneste ved hodepine
Telefon: 72 57 51 47

Pasientnummer _____

HEADACHE and PITUITARY ADENOMA

Dato brev:

Dato oppringt:

| | | | | | |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |

Pasient initialer

(første bokstav i første og siste navn)

| | | | |
|----------------------|----------------------|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|----------------------|----------------------|

Pasientnummer

| | | | | | |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|

Kjønn

mann 1, kvinne 2

| |
|----------------------|
| <input type="text"/> |
|----------------------|

Alder i dag

| | | | |
|----------------------|----------------------|----------------------|----|
| <input type="text"/> | <input type="text"/> | <input type="text"/> | år |
|----------------------|----------------------|----------------------|----|

Hva var årsaken til at MR ble tatt?

| |
|--|
| |
| |

Ble svulsten oppdaget som et ledd i en utredning av hodepine?

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

| |
|--|
| |
| |

Benytter du hormonsubstitusjon nå?

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Hvilken?

| Medikamentnavn | Vanlig dose pr. dag |
|----------------|---------------------|
| | |
| | |

Faste medisiner for annen sykdom

| Medikamentnavn | Vanlig dose pr. dag |
|----------------|---------------------|
| | |
| | |

Medisin du tar i perioder (utenom hodepine)

| Medikamentnavn m/evt. årsak | Dose pr. dag/måned |
|-----------------------------|--------------------|
| | |
| | |

Har du, eller har du hatt noen sykdommer vi bør vite om?

| |
|--|
| |
| |

Jobb og/eller studier totalt

| | | |
|--------|----------------------|---|
| 100% | <input type="text"/> | 1 |
| 50-99% | <input type="text"/> | 2 |
| < 50% | <input type="text"/> | 3 |

Hvis <100%, angi årsak

35

100% uføretrygdet

| |
|----------------------|
| <input type="text"/> |
|----------------------|

Midlertidig permittert

| |
|----------------------|
| <input type="text"/> |
|----------------------|

50-90% uføretrygdet

| |
|----------------------|
| <input type="text"/> |
|----------------------|

Arbeidsledig

| |
|----------------------|
| <input type="text"/> |
|----------------------|

Sykmeldt % _____

| |
|----------------------|
| <input type="text"/> |
|----------------------|

Annet, spesifiser

| |
|----------------------|
| <input type="text"/> |
|----------------------|

Hjemmearbeidende

| |
|----------------------|
| <input type="text"/> |
|----------------------|

| |
|--|
| |
| |

Er du blitt uføretrygdet pga hodepine?

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Er det noen i familien med plagsom hodepine?

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

(Flere avkrysningsmuligheter)

| | | |
|---------------|----------------------|---|
| søsken | <input type="text"/> | 1 |
| barn | <input type="text"/> | 2 |
| foreldre | <input type="text"/> | 3 |
| besteforeldre | <input type="text"/> | 4 |

(førstegrads slektninger)

Når hadde du hodepine første gang? (rett før)

Var du plaget med hodepine det siste året før operasjonen /
behandlingsstart / diagnosetidspunkt?

Hodepinemønster før:
(flere avkrysningsmuligheter)

Anfallsvis kraftig hodepine

Med kvalme eller oppkast

Hodepine < 15 dager pr. måned
Hodepine > 15 dager pr. måned
Helt hodepinefri mellom anfall

Tok du smertestillende mot hodepinen?

Hvis ja, hvor ofte _____

Endret hodepinen karakter etter oppstart av behandling
behandlingen av hypofysesvulst?

Verre Startet Bedre Uendret

Beskriv _____

Er du plaget med hodepine etter operasjonen / behandlingen /
nå for tiden ?

Hodepinemønster etter:
(flere avkrysningsmuligheter)

Anfallsvis kraftig hodepine

Med kvalme eller oppkast

Hodepine < 15 dager pr. måned
Hodepine > 15 dager pr. måned
Helt hodepinefri mellom anfall

Har du fått en hodepinediagnose fra lege/spesialist?

Nevrolog Fastlege

Hvilken diagnose? _____

Har du flere typer hodepine?

Hvis ja, hvor mange typer? _____

Hvilke? _____

Egendiagnose av hodepine _____

Manglende samsvar mellom pasientinformasjon og journal?

Kommentar _____

HUNT (samme som ble stilt i Helse undersøkelsen i Nord-Trøndelag)

1) Har du vært plaget av hodepine det siste året?

Hvis ja, hva slags hodepine? Migrene
Annen

2) Omtrent antall dager pr. måned med hodepine

Mindre enn en dag 7-14 dager
1-6 dager Mer enn 14 dager

3) Hvor sterk er hodepina vanligvis?

Mild (hemmer ikke aktivitet)
Moderat (hemmer aktivitet)
Sterk (forhindrer aktivitet)

4) Hvor lenge varer hodepina vanligvis?

Mindre enn 4 timer
4 timer til 1 døgn
1-3 døgn
Mer enn 3 døgn

5) Er hodepina vanligvis preget av eller ledsaget av

Bankende/dunkende smerte?
Pressende smerte?
Ensidig smerte?(høyre/venstre)
Forverring ved moderat fysisk aktivitet?
Kvalme og/eller oppkast?
Lys- og lydskjyhet?

6) Før eller under hodepina; kan du ha hatt forbigående

Synsforstyrrelse?
Nummenhet?

7) Angi hvor mange dager du har vært borte fra arbeid eller skole dager
siste måned på grunn av hodepine:

Medisinbruk for hodepine:

| Medikamentnavn | Antall tbl/ sprøyter/sprayer i gj.snitt per hodepinedag | Hypppighet (antall dager pr. mnd) | Effekt |
|----------------|--|---|--------|
| | | | |
| | | | |
| | | | |

Effekt: :0-ingen, 1-dårlig, 2-middels, 3-god

Har du prøvd forebyggende medisiner mot hodepine?

| Medikamentnavn | Dose | Effekt |
|----------------|------|--------|
| | | |
| | | |
| | | |

GENERELLE OPPLYSNINGER FRA JOURNAL

Data innsamlet dato

| | | | | | |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|

Diagnose/ operasjonskoder:

| | | | | | |
|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |

Hodepine nevnt i journalnotat

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Hodepine før behandlingsstart

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Kommentar

Hodepine etter behandling

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Kommentar

HODEPINEDIAGNOSE av nevrolog

Hovedhodepine: _____ ICHD _____

Tilleggshodepine: _____ ICHD _____

Blodtrykk før behandlingsstart

| | | | | | | | | |
|----------------------|----------------------|----------------------|----------------------|---|----------------------|----------------------|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | / | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|----------------------|----------------------|---|----------------------|----------------------|----------------------|----------------------|

Blodtrykk ved siste kontroll

| | | | | | | | | |
|----------------------|----------------------|----------------------|----------------------|---|----------------------|----------------------|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> | / | <input type="text"/> | <input type="text"/> | <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|----------------------|----------------------|---|----------------------|----------------------|----------------------|----------------------|

Type tumor:

Ikke hormonproduserende

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Hormonproduserende

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

GH

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

TSH

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

ACTH

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Prolaktin

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

LH/FSH

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Endocrine variabler:

Hormon mangel på diagnose tidspunkt?

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Om ja, hvilke hormoner: _____

Hormon mangel nå?

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Om ja, hvilke hormoner substitueres: _____

Lokale nevrologiske effekter:

Syn: Redusert syn

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Redusert synsfelt

| | |
|----------------------|----------------------|
| <input type="text"/> | <input type="text"/> |
|----------------------|----------------------|

Andre nevrologiske utfall nevnt i journalen: _____

Tid mellom diagnostisk MRI og første behandling

| | | |
|----------------------|----------------------|---------|
| <input type="text"/> | <input type="text"/> | dager |
| <input type="text"/> | <input type="text"/> | måneder |
| <input type="text"/> | <input type="text"/> | år |

Behandling:

- 1) **Medikamentbehandling alene**
- 2) **Operasjon**
(med eller uten preoperativ medikamentbehandling)
- TSS (operert via nesen) (alene)
 - Kraniotomi (alene)
 - Begge deler
- 3) **Strålebehandling**
Konvensjonell strålebehandling
Gammakniv
- 4) **Ingen behandling hittil**

Antall måneder siden siste behandling

Antall re-operasjoner

Årsak _____

Proliferative index/ki-67 (proliferation status):

Low: < 3%

High: > 3%

Immunoreaktivt p53 (marker for aggressive growth)

Low: < 1%

High: > 3%

Første MR = diagnose tidspunkt

Tumor diameter **mm**

Løfting av diafragma sella? (ja/nei)

Trykk mot synsnerveapparatet? (ja/nei)

Innvekst i sinus cavernosus? (ja/nei)

Sella turcica destruksjon? (ja/nei)

Hardy grade – om svulsten vokser utenfor hypofysen

Intracellar (ja/nei)

Extracellar/suprasellar (ja/nei)

Invasiv (ja/nei)

Dato for siste MR kontroll

Tumor diameter **mm**

Løfting av diafragma sella? (ja/nei)

Trykk mot synsnerveapparatet? (ja/nei)

Innvekst i sinus cavernosus? (ja/nei)

Hardy grade – om svulsten vokser utenfor hypofysen

Intracellar (ja/nei)

Extracellar/suprasellar (ja/nei)

Invasiv (ja/nei)

Sella turcica destruksjon? (ja/nei)

149

MR 1: *111111*

Diameter

• Største diameter coronarplan

41

• Diameter coronarplan 90 grader på største

36

• Diameter sagittalplan

29

Modified Hardy grade:

I: ≤ 10 mm in sella turcica (microadenoma)

II: 10-20 mm, suprasellar extent within 10 mm of planum sphenoidale

III: 20-40 mm, suprasellar extent up to 30 mm, elevates or fills anterior third ventricle

IV: ≥ 40 mm, extent far beyond sellar space with lateral or multiple expansions

Løfter diafragma sella (convex)



Trykk mot synsnerveapparatet



Innvekst i sinus cavernosus



Utvidelse av sella turcica



Gjennomvekst av gulvet i sella til sphenoidalsinus



MR 2: *111111*

Diameter

• Største diameter coronarplan

7

• Diameter coronarplan 90 grader på største

7

• Diameter sagittalplan

5

Modified Hardy grade:

I: ≤ 10 mm in sella turcica (microadenoma)

II: 10-20 mm, suprasellar extent within 10 mm of planum sphenoidale

III: 20-40 mm, suprasellar extent up to 30 mm, elevates or fills anterior third ventricle

IV: ≥ 40 mm, extent far beyond sellar space with lateral or multiple expansions

Løfter diafragma sella (convex)



Trykk mot synsnerveapparatet



Innvekst i sinus cavernosus



Utvidelse av sella turcica



Gjennomvekst av gulvet i sella til sphenoidalsinus

