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Pituitary adenoma and non-acute headache: Is there an association, and does treatment help?

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Abstract:

Objective: Headache is a controversial indication for treatment of pituitary adenoma. We sought to study the possible relationship between pituitary adenomas and headache along with the symptomatic effects of treatment.

Methods: 201 patients with pituitary adenoma underwent structured telephone interviews addressing current and prior headache complaints. Clinical variables and headache history were retrieved from medical records. Headache prevalence among patients was compared to a regional population-based cohort.

Results: Headache suffering prior to the pituitary adenoma diagnosis was higher than in the general population ($p<0.001$). At follow-up, overall prevalence was lower ($p<0.001$), but chronic headache was more prevalent ($p= 0.001$) than in the general population. With the exception of family history, no associations between headache and clinical or radiological variables were identified. 77% of headache sufferers reported improvement and5 % reported worsening while 11 % reported new headaches at follow-up. Operated patients with non-functional adenoma more often reported improvement (85%) than non-operated patients (58%) ($p=0.042$).

Conclusion: In a cohort with both treated and untreated patients with pituitary adenoma headache prevalence is low compared to the general population. We found no link between clinical or radiological variables and headache. Even though a higher proportion of operated patients report symptomatic relief, the majority of non-treated patients also improved. We believe that the rather unpredictable dynamics of headache over time and the lack of predictive and modifiable tumor related variables associated with headache or relief we believe this weakens headache as a sole indication for pituitary adenoma treatment.

Introduction

Headache is a prevalent disorder; the one-year prevalence of "headache suffering" is 37% in the general population.[1] Pituitary adenomas, especially microadenomas are also common, and a systematic review found a pooled prevalence of 16.7% across studies.[2] More available and improved imaging techniques have increased the observed incidence rates of pituitary adenomas, [3] and both studies in Europe and in the USA report of increasing prevalence.[4-6]

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. There are so far no controlled studies comparing headache symptoms between treated and untreated patients. Due to the weak evidence and contradictory findings from prior, often small and retrospective studies, [7-12] headache alone is still a controversial indication for treatment of pituitary tumors, despite rather good results in published surgical case series.[3] Current clinical guidelines for surgery of pituitary incidentaloma nevertheless suggest that surgery may be considered for patients suffering from "unremitting headaches",[13] but criteria to select and identify who may benefit from surgery are lacking.

To explore the possible relationship between pituitary adenomas and headache, we performed a retrospective cohort study with follow-up of patients diagnosed with pituitary adenoma. We acquired data on previous and current headache complains from structured patient interviews and from retrospective review of hospital medical records. Headache prevalence among pituitary adenoma patients was compared to data from a comprehensive population based health study carried out in a Norwegian county in our hospital's geographical catchment region.

Methods

Study population

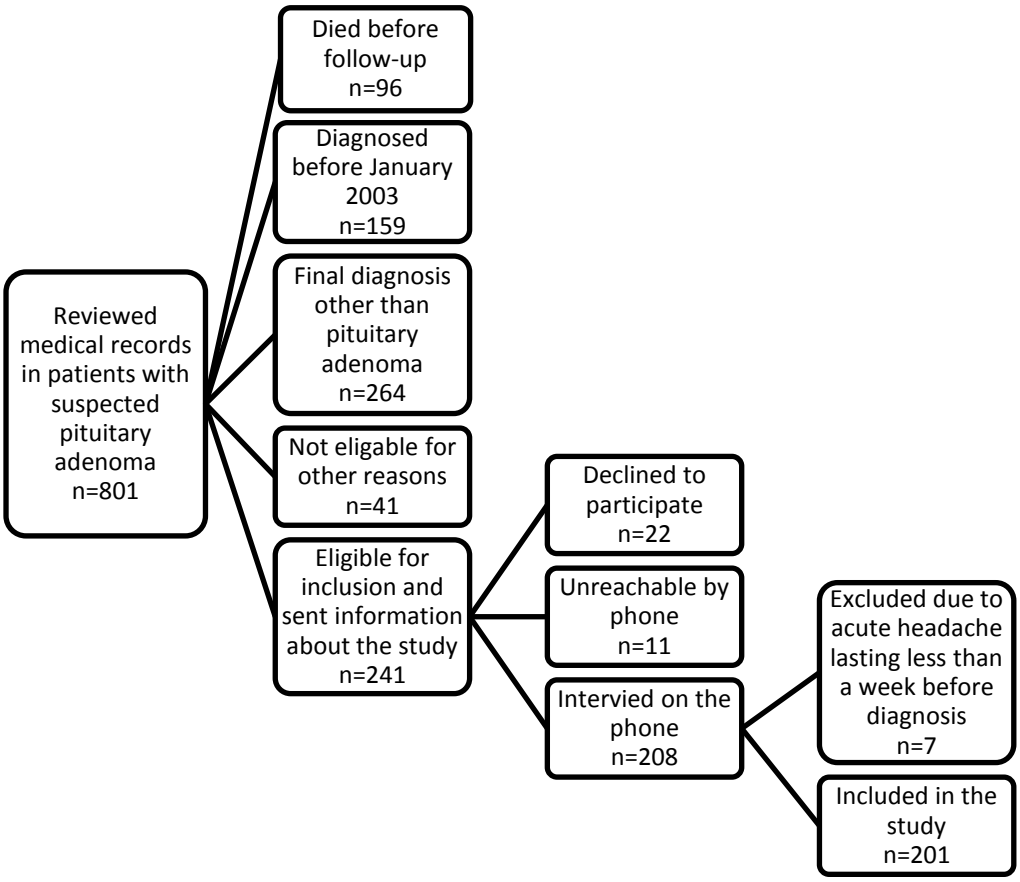
All patients at St. Olavs University Hospital, Trondheim, Norway, diagnosed with pituitary adenoma during the 10 year period from January 2003 through December 2013 were screened for inclusion in the study. Patients under 18 years of age (n=6), patients suffering from severe dementia or psychiatric illness (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 not found eligible for inclusion.

Medical records (n= 801) with the ICD-10 diagnostic codes (D35.2, D44.3, E22.0, E22.1, E22.8, E22.9, E23.0, E23.7, E24.0 and R90.0) or operation codes (Transsphenoidal exploration ,extirpation or resection) were screened to identify all patients referred to our hospital with pituitary adenomas in the study period.

Data collection

As seen in Figure 1, 241 patients were found eligible for inclusion, 208 (86.3%) agreed to participate and 201 were included in the study. All eligibles were sent a letter dated March 2014 with information about the study. 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. All interviews and reviews were conducted by an experienced research nurse (GBG). Study variables concerning the treatment of the pituitary tumors, type of tumor, endocrine variables, MRI variables and information concerning headache were retrieved from review of hospital medical records.

FIGURE 1 Flow chart



Headache assessment

To be classified as a headache sufferer at the time of diagnosis, we decided that previous headache had either to be documented in the medical records, or that headache suffering the year preceding the diagnosis had to be clearly stated by the patients in the interview. Current headache was defined according to the validated question from the local population based health study (HUNT): "Have you suffered from headaches during the last year?"[14,15]

Acute headaches lasting less than a week before the diagnosis were excluded since pituitary apoplexy is a known cause of headache and could act as a confounder.[12,16,17] In six patients, a bleeding/apoplexy was seen on the initial MRI, making pituitary apoplexy the likely cause of the acute headache. In one patient an acute sinus infection was the likely cause of the acute headache.

As seen in figure 1, these 7 patients with acute headaches before diagnosed with pituitary tumours were excluded, leaving 201 patients for analyses.

Hormone assessment

Adenomas were divided into functional or non-functional adenomas based on clinical and biochemical assessments. Functional adenomas were subdivided based on secretion of prolactin, growth hormone or ACTH. Hormone deficiencies were classified based on the interpretation of laboratory tests performed by the treating clinicians at the time. Secondary hyperprolactinemia believed to result from pituitary stalk compression in patients without prolactinomas was recorded from medical records. Current hormone substitution was recorded from the patient interviews.

Radiological assessment

A consultant neurosurgeon (OS) reviewed all MRIs blinded for other data. The diagnostic and the most current MRIs were reviewed. Median time between the diagnostic MRI and the patient interview was 65 months (range 5 to 120 months). Median time from the latest MRI and patient interview was 12 months (range 0 to 111 months). 186 (93%) of the diagnostic and 187 (93%) of the latest MRIs were available for assessment. In 7%, MRIs from time of diagnosis were not accessible and the descriptions from the radiologist were used.

The tumors were classified into four grades according to the modified Hardy's grading system.[18] Tumors 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).[19] The volumes of the tumors were calculated as $\pi/6 \cdot d_1 \cdot d_2 \cdot d_3$. We also assessed lifting of the sellar diaphragm (Y/N), radiological compression of the optic nerves or

chiasm (Y/N), growth into sinus cavernosus (Y/N), expansion of sella turcica (Y/N) and growth through the floor into the sphenoidal sinus (Y/N).

Healthy controls

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.[20] 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. [1] The overall age-adjusted 1-year headache prevalence was 43% in women and 30% in men, a total prevalence of 37%. Individuals who answered "yes" to the question "Have you suffered from headache during the last 12 months?" were classified as headache sufferers.[21] Answering the subsequent 13 headache questions enabled diagnosing migraine according to the International Classification of Headache Disorders (ICHD-II).[1,22] The headache questionnaire and questionnaire-based diagnoses have previously been validated.[14,15]

Statistical analysis

Statistical analysis of the clinical data was performed using IBM SPSS Statistics 21 for Windows. Results were considered significant at a level of $p<0.05$. Q-Q-plots were used to assess normal distribution of data. Median and rage is presented for skewed data. Prevalence of headache in patients with pituitary adenomas was compared to data from HUNT 3,[1] adjusted for age and sex. A Chi-square goodness-of-fit was used to compare our adenoma population to the HUNT population. Categorical variables were compared using Chi-square test. Mann-Whitney U test was used to check for possible associations between tumor sizes and headache.

Ethics

Data collection was approved by the Regional Committee for Medical and Health Research Ethics for Health Region Mid-Norway and adhered to the guidelines of the Helsinki Declaration.[23] Answering the questions on the phone served as an affirmation of informed consent. The expenses were covered by the Norwegian Advisory Unit on Headaches.

Results

90 (45%) of the included patients were men and 111 (55%) women. Mean age was 61 [±15] years in males and 50 [±15] years in females. At diagnosis the prevalence of "non-acute headache" was 101/201 (50%) and at follow-up the prevalence of headache suffering was 54/201 (27%).

The age and sex-adjusted prevalence of non-acute headache before being diagnosed with pituitary adenomas was 50%, which is significant higher than in the general population (HUNT 3 study), 50% vs. 37%, $p<0.001$.[1,21] The age and sex-adjusted prevalence of headache the last year before follow-up was significantly lower than in the general population in the HUNT 3 study, 21% vs. 37%, $p<0.001$.[1]

TABLE 1. Main symptoms that lead to the diagnostic MRI, N(%)

Symptom	**No. of patients**
Headache	25 (12)
Visual problems	31 (15)
Sex hormone related*	39 (19)
Other symptoms including symptoms of hormonal disturbances †	50 (25)
Neuroimaging for other conditions, incidental finding ‡	56 (28)
Total	**201(100)**

* menstrual cycle, lactation, libido, impotence

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

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

As seen in Table 1, 12% of the patients had headache as the main symptom leading to the diagnostic MRI. A family history of headache was significantly more common in headache sufferers than in patients without headaches, 51% vs. 35%, p=0.026.

TABLE 2. Non-acute headache and MRI characteristics from 201 patients at diagnosis and 187 patients at follow-up

	Headache at diagnosis	Headache in controls with other MRI characteristics	p-value	Current headache	Headache in controls with other MRI characteristics	p-value
Modified Hardy Grade*						
< 10 mm in sella turcica	26/60 (43)	74/139 (53)	0.200	15/51 (29)	36/136 (26)	0.688
0-20 mm, supra-sellar extent within 10 mm of planum sphenoidale	33/64 (52)	N/A		7/36 (19)	N/A	
20-40 mm, supra-sellar extent up to 30 mm, elevates or fills anterior third ventricle	18/38 (47)	N/A		4/7 (57)	N/A	
40 mm, extent far beyond sellar space with lateral or multiple expansions	23/37 (62)	77/162 (48)	0.108	4/22 (18)	47/165 (28)	0.308
Other MRI characteristics†						
Lifting of the sellar diaphragm	75/139 (54)	26/61 (43)	0.140	11/45 (24)	40/142 (28)	0.625
Compression of optic nerve(s)	28/55 (51)	73/145 (50)	0.943	2/8 (25)	49/179 (27)	0.883
Growth into cavernosus sinus	26/51 (51)	75/149 (50)	0.937	9/40 (23)	42/147 (29)	0.445
Expansion of sella turcica	54/94 (57)	47/106 (44)	0.064	7/40 (18)	44/147 (30)	0.118
Growth into the sphenoidal sinus	21/34 (62)	80/166 (48)	0.149	4/14 (29)	47/173 (27)	0.910
No tumour-remnant	N/A	N/A	N/A	21/73 (29)	30/114 (26)	0.713

*missing MRI data in 2 patients, †missing MRI data from 1 patient
N/A: Not applicable

As seen in Table 2, there appears to be no clear dose-response associations between headache and assessed MRI characteristics. A subgroup analysis in patients with non-functional adenomas gave

similar results (data not shown). There were also no differences in largest tumor diameters or calculated tumor volumes for patients with versus without headaches before being diagnosed, 17.0 [1-56] mm vs. 14 [0-47] mm, p=0.192 and 1.62 [1-37.83] ml vs. 1.32 [0-28.82] ml, p=0.184. Nor were there differences in the largest tumor diameters or calculated tumor volumes from the most recent MRIs in patients with versus without current headache, 6.0 [0-29] mm vs. 7.0 [0-45] mm, p=0.329 and 0.07 [0-6.56] ml vs. 0.08 [0-12.20] ml, p=0.442.

Headache was not more common in patients diagnosed with hormone deficiencies compared to patients with no known hormone deficiencies, at diagnosis 34/67 (51%) versus 67/134 (50%), p=0.921 or at follow-up 27/79 (34%) vs. 27/122 (22%), p=0.060.

Presumed secondary hyperprolactinemia due to pituitary stalk compression as seen in 39 patients was not associated with headache before diagnosis (p=0.973) or at follow-up (p=0.369).

TABLE 3 Headache change vs. treatment, n (%)

	Operated patients n=124	**Non-operated patients n=77**	Medication only* n=49	No treatment† n=28	**Total n=201**
Non-acute headache at diagnosis	68/124 (55)	33/77 (43)	21/49 (43)	12/28 (43)	101/201 (50)
Resolved: Non-acute headache at diagnosis and no headache the last year	40/68 (59)	18/33 (55)	12/21 (57)	6/12 (50)	58/101(57)
Improved: Non-acute headache at diagnosis and improvement in experienced headache the last year	16/68 (24)	4/33 (12)	3/21 (14)	1/12(8)	20/101 (20)
Unchanged: Non-acute headache at diagnosis and headache the last year	8/68 (12)	10/33 (30)	5/21 (24)	5/12 (42)	19/101 (18)
Worse: Non-acute headache at diagnosis and worsening in experienced headache the last year	4/68 (6)	1/33 (3)	1/21 (5)	0 (0)	5/101 (5)
New headache: No headache at diagnosis, but headache at follow-up	5/56 (9)	6/44 (14)	3/28 (11)	3/16 (19)	11/100 (11)
Current headache:	33/54	21/54	12/54	9/54	54/201 (27)

*48 of 49 patients had prolactinomas, and 1 patient had a low-grade GH-producing adenoma not operated due to severe comorbidity. †25 of 28 patients had NFA, 1 patient had a low grade acromegaly, and 2 patients with microadenoma and long-term hyperprolactinemia were classified as prolactinomas, but were not treated so far.

As seen in Table 3, 58 (57%) of the 101 patients with non-acute headaches at diagnosis no longer suffered from headaches at follow-up, and 20 (20%) reported significant improvement at follow-up. Thus, in total 78/101 (77%) reported resolved or improved headaches. Although a statistical trend was seen, improvement or cure of headaches was not significantly more common among operated patients than among non-operated patients, 56/68 (82%) versus 22/33 (64%) (p=0.078). Moreover, 5 % (6% of operated) reported worsening of previous headaches and 11 % (9 % of operated) reported new headaches at follow-up.

TABLE 4. Headache change vs. type of adenoma, n (%)

Type of adenoma	**Non-functional adenomas**			**Functional adenomas**			
	Total	Operated	Non-operated	**Total**	Acromegaly	Mb. Cushing	Prolactinoma
Non-acute headache at diagnosis	53/102 (52)	41/77 (53)	12/25 (48)	48/99 (48)	16/25 (64)	9/21 (43)	23/53 (43)
Resolved	31 (58)	25 (61)	6(50)	27 (56)	8 (50)	6 (67)	13 (57)
Improved	11 (21)	10 (24)	1 (8)	9 (19)	5 (31)	1 (11)	3 (13)
Unchanged	9 (17)	4 (10)	5 (42)	9 (19)	2 (13)	1 (11)	6 (26)
Worse	2 (4)	2 (5)	0	3 (6)	1 (6)	1 (11)	1 (4)
New headache	5/49 (10)	2/36 (6)	3/13 (23)	6/51 (12)	2/9 (22)	1/12 (8)	3/30 (10)
Current headache	27/102	18/77	9/25	27/99	10/25	4/21	13/53

As seen in Table 4 there were no apparent overall difference in headache prevalence between patients with functional and non-functional adenomas at diagnosis or at follow-up (p=0.622 and p=0.898). The highest headache prevalence was reported among patients with GH-secreting adenomas, but still not significantly higher than among other patients at diagnosis (p=0.142) or at follow-up (p=0.113). In total 42/53 (79%) of patients with non-functional adenomas report resolved or improved headaches at follow-up. In patients with functional adenomas 36/48 (75%) report resolved or improved headaches at follow-up. In patients with non-functional adenomas, improvement or cure of headaches was significantly more common among operated patients, 35/41 (85%) versus 7/12 (58%) (p=0.042).

TABLE 5. Sub-classification of current headaches compared to the general population, n (%)

	Operated patients n=124	**Non-operated patients n=77**	**Total n=201**	**HUNT 3 n=39690**
Migraine the last year (self-considered migraine)	4 (3)	4 (5)	8 (4)	3059 (8)
Migraine according to 2010 diagnostic (restrictive) criteria*	4 (3)	10 (13)	14 (7)	4404 (12)
Non-migrainous headache the last year	29 (23)	18 (23)	47 (23)	9329 (24)
Chronic headache >14 days per month	12 (10)	8 (10)	20 (10)	973 (3)

* ICHD-II 2004 [22] except duration of headache, more closely described in reference.

Sub-classification of current headaches is presented in Table 5. There was no significant difference between operated and non-operated patients in terms of types of current headaches, except when assessing headache symptoms according to the restrictive 2010 ICHD-II diagnostic criteria.[1] The prevalence of migraine among non-operated patients is similar to in the HUNT 3 population (13% vs. 12%), but operated patients report significantly less seldom migraine than non-operated patients (3% vs. 13%, p=0.014).

The prevalence of current chronic headache is significantly higher in patients with pituitary adenomas compared to the general population (HUNT 3) (10% vs. 3%, $p<0.001$).[1]

Discussion

In the present study we found that approximately one in four patients diagnosed with or treated for pituitary adenomas report that they suffered from headaches the last year before follow-up. Curiously, this prevalence is lower than in an age- and sex-adjusted general population.[1] With the exception of family history of headache we were not able to identify any clinical, endocrinological or radiological factors associated with headache prior to or after treatment. Although retrospective assessment of headaches from medical records and interviews are prone

to bias, we found that headache prevalence was significantly higher than in the general population at diagnosis. Approximately three out of four patients with headaches at diagnosis reported relief or improvement at follow up. Patients with non-functional adenomas who underwent surgery more often reported improvement or relief, but even among untreated patients 58% reported resolved or improved headaches at follow up. In addition, 5% reported worsening of previous headaches and 11% reported new headaches at follow-up. We believe that the unpredictable dynamics of headache symptoms over time in this population and the lack of an apparent "dose-response" association between headache and tumour related variables weakens headache as a sole indication for pituitary adenoma treatment.

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.[12] A retrospective study in 4050 patients operated for pituitary adenomas reported that 69% experienced headaches before surgery.[18] However, 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. Selection of the most appropriate headache question is important both for correct prevalence estimation, but can also be important for assessing possible biological association with pituitary disease. Since headache is so prevalent in the general population many patients with pituitary adenomas will suffer from headaches due to unrelated causes. We found that headache symptoms the last year was not higher than in controls at follow-up, but nevertheless found that chronic headache (>14 days/month) was higher in patients with pituitary tumors. Chronic headache more than 14 days per month the past months might be easier to recall than fewer days. Thus, future studies assessing possible biological relationships between pituitary disease and headache should perhaps assess chronic headache.

Levy et al. classified 84 patients with pituitary adenomas suffering from headaches and found that 87% fulfilled the accepted criteria of primary headache diagnoses according to ICHD-II criteria.[9] When assessing the headache symptoms in our data according to the restrictive migraine criteria,[1] operated patients more seldom reported migraine. A possible factor contributing to this difference might be that 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, and the prevalence drops markedly after the age of 60.[1]

We found that a family history of headache was significantly associated with headache among patients with pituitary adenomas. The association with family history and headache exemplifies that non tumor related factors can explain headaches among some patients with pituitary disease. These results are supported by other studies. Levy et al. found a strong association with family history of headache and pituitary-associated headache.[8] An association between pituitary tumor and a family history of headache has also been found by Schankin et al.,[11] but not Gondim et al.[7] It has also been suggested that pituitary tumors may lower the threshold for migraines and that phenotypic family headaches might be important.[3]

Headache is a common cause for undergoing diagnostic cerebral MRIs that may lead to the incidental discovery of pituitary adenomas.[24] A recent retrospective study found that 24% of patients with pituitary tumours had headache as their chief complaint before surgery.[25] In the present study 12% of our patients had headache as the main symptom leading to the diagnostic MRI, presumably contributing to the higher prevalence of headache than in the general population at diagnose. The availability of MRI is exceptionally high in Norway and the number of benign extra-axial brain tumors due to incidental findings are therefore rising.[26]

More than half of the patients in this study were cured from their previous headaches at follow-up. This improvement was assessed retrospectively and not documented in headache diaries. Although improvement in headache following pituitary adenoma treatment could suggest a link between the tumor and the headache, it is difficult to control for possible confounding variables or the natural history.[9] Patients often seek medical advice, are diagnosed and sometimes treated in periods with high symptom burdens so improvements over time may also be due to regression to the mean. In addition, headache prevalence was expected to fall over time due to aging alone.[27,28] Although not statistically significant, there was a trend towards more improvements of headaches among operated patients. However, improvement over time was also most often seen in untreated patients as well. Also, comparisons across groups may be hampered by differences in reasons for being diagnosed with the pituitary adenoma in the first place and age differences between groups. Interestingly, among patients with non–functioning adenomas relief or improvement of headache was significantly more common in operated patients, a finding that could suggest a biological ling between headache and pituitary adenomas. In contrast to the functional adenomas, headache may be used as an indication for surgery in this group. Yet, a placebo effect from surgery can not be ruled out.

Still, a placebo effect from surgery is also not unlikely. Several other studies have reported improvement in headaches after treatment but acknowledge possible contributing factors, including the long time before follow up.[9-11] Fleseriu et al. have published remarkable results in a retrospective study of 41 patients with small sellar lesions and severe treatment refractory headaches. Of the 30 patients with microadenomas who underwent transsphenoidal surgery 87% reported relief of headache symptoms after surgery. For the functional adenomas, symptom relief

correlated to hormonal remission. Still, the authors acknowledge that a significant placebo effect was not unlikely.[3]

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.[8] Still, to our knowledge, no prospective clinical study has yet demonstrated a correlation between tumor headache and endocrine function. Even so, headache is a classic feature of growth hormone-secreting pituitary tumors, and somatostatin can have an analgesic effect on acromegaly associated headache. Yet, in this study the incidence of headache was not significantly higher in patients with acromegaly, as also reported by others.[29] It is also known that dopamine agonist therapy may improve migraine as well as markedly exacerbate headache in treatment of prolactinomas.[24] We found no hormone related variables that were associated with headache either before the diagnosis or at follow-up. However, hormone deficiencies were classified based on the interpretation of laboratory tests stated in the medical records and not assessed systematically or prospectively. In several cases, the preoperative endocrine assessment was limited to exclusion of significant hypocortisolism and hyperprolactinemia, and data on particularly the growth hormone axis can also be insufficient postoperatively. In analyses, we also did not take into account additional medical therapy or radiotherapy given to patients with functional adenomas to obtain biochemical remission.

Early studies found that headache in patients with intracranial tumors is related to tumor size and dural stretch,[30,31] but these findings have been questioned in later studies.[8] A recent retrospective review of 1015 patients with sellar lesions (66% adenomas) found that patients with gross total resection (GTR) more often achieved postoperative headache improvement, in line with the

hypothesis that the underlying cause of headache is mass effect.[25] However, another recent study found that headaches were equally frequent in patients with microadenomas and macroadenomas.[29] In our study, neither residual tumor nor tumor size was associated with headache. Increased intrasellar pressure has also been postulated as cause of headache in pituitary adenoma.[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 could be the speed of tumor growth and the ability of the sellar walls to modulate this growth.[7] We found no association between cavernous sinus invasion and headache in the present study. Schankin et al. 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 tumor tissue.

Study strengths and limitations

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, and within the same hospital catchment region. Non-functional adenomas were the most prevalent in our study population and there were relatively few prolactinomas. The high proportion of non-functional adenomas is seen in most studies of headache in patients with pituitary tumours.[3,10,11] Still, this differs from large population based studies[2,4,5] where prolactinomas are the most common. Microprolactinomas are usually treated at local hospitals in contrast to the other pituitary tumors, and are therefore underrepresented in this patient cohort from a tertiary centre.

All the interviews were done by the same experienced interviewer and the images were interpreted by the same neurosurgeon, blinded for other data. The the combined method of

retrospective review of hospital medical records and follow-up patient interviews was chosen to assess the relevant hospital-based population within a manageable timeframe, while minimizing selection and information bias.

The main limitation is the retrospective retrieval of some variables which is challenged by missing data and danger of misinterpretations. Patients are at times inconsistent when reporting past headaches due to recall bias and the self-improvement effect. We therefore used a synthesis of recalled data and data from medical records for assessing the headache prevalence at diagnosis. Data on prevalence before diagnosis and headache change over time is therefore weaker than data on current complaints. Ninety-six patients died before inclusion, and the few patients who declined to participate increase the risk of a non-responder bias.
Pituitary deficiency was not possible to evaluate properly retrospectively and relies on unsystematically and often uncertain data from medical records. 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 both false positive and negative statistical findings due to chance or lack of power.

Conclusion

In conclusion, we found that the prevalence of headaches among patients harbouring both treated and untreated pituitary adenomas is surprisingly low compared to the general population. Together with the unpredictable dynamics of headache complaints over time, and lack of tumor related variables associated with headache or relief, we argue that headache as a sole indication for treating pituitary adenomas is questionable.

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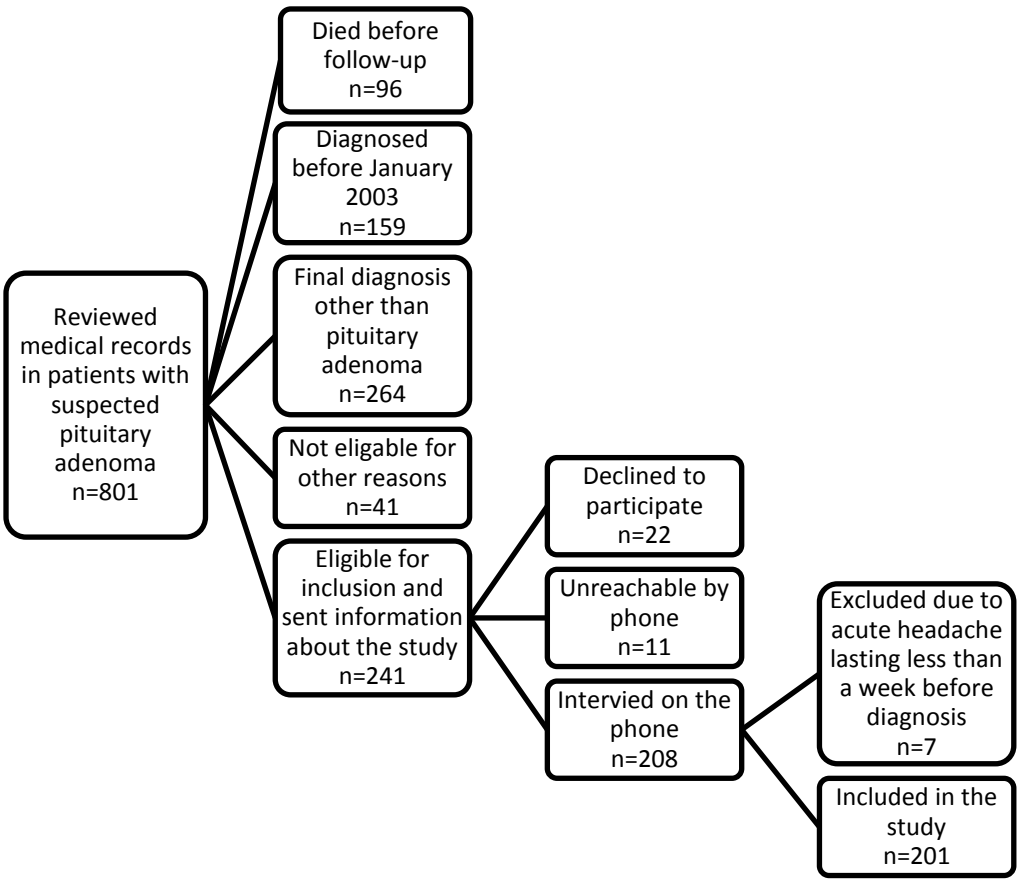

FIGURE 1 Flow chart

TABLE 1. Main symptoms that lead to the diagnostic MRI, N(%)

Symptom	**No. of patients**
Headache	25 (12)
Visual problems	31 (15)
Sex hormone related[*]	39 (19)
Other symptoms including symptoms of hormonal disturbances [†]	50 (25)
Neuroimaging for other conditions, incidental finding [‡]	56 (28)
Total	**201(100)**

[*] menstrual cycle, lactation, libido, impotence

[†]pain, fatigue, exhausted, dizziness, unwell, sleep problems, weight increase, body change, acne, thirst, nausea

[‡] stroke/TIA, fall, fractures, syncope, eye/ear/neck/back problems, abnormal blood test

TABLE 2. Non-acute headache and MRI characteristics from 201 patients at diagnosis and 187 patients at follow-up

	Headache at diagnosis	Headache in controls with other MRI characteristics	p-value	Current headache	Headache in controls with other MRI characteristics	p-value
Modified Hardy Grade*						
< 10 mm in sella turcica	26/60 (43)	74/139 (53)	0.200	15/51 (29)	36/136 (26)	0.688
0-20 mm, supra-sellar extent within 10 mm of planum sphenoidale	33/64 (52)	N/A		7/36 (19)	N/A	
20-40 mm, supra-sellar extent up to 30 mm, elevates or fills anterior third ventricle	18/38 (47)	N/A		4/7 (57)	N/A	
40 mm, extent far beyond sellar space with lateral or multiple expansions	23/37 (62)	77/162 (48)	0.108	4/22 (18)	47/165 (28)	0.308
Other MRI characteristics†						
Lifting of the sellar diaphragm	75/139 (54)	26/61 (43)	0.140	11/45 (24)	40/142 (28)	0.625
Compression of optic nerve(s)	28/55 (51)	73/145 (50)	0.943	2/8 (25)	49/179 (27)	0.883
Growth into cavernosus sinus	26/51 (51)	75/149 (50)	0.937	9/40 (23)	42/147 (29)	0.445
Expansion of sella turcica	54/94 (57)	47/106 (44)	0.064	7/40 (18)	44/147 (30)	0.118
Growth into the sphenoidal sinus	21/34 (62)	80/166 (48)	0.149	4/14 (29)	47/173 (27)	0.910
No tumour-remnant	N/A	N/A	N/A	21/73 (29)	30/114 (26)	0.713

*missing MRI data in 2 patients, †missing MRI data from 1 patient
N/A: Not applicable

TABLE 3 Headache change vs. treatment, n (%)

	Operated patients n=124	**Non-operated patients n=77**	Medication only* n=49	No treatment† n=28	**Total n=201**
Non-acute headache at diagnosis	68/124 (55)	33/77 (43)	21/49 (43)	12/28 (43)	101/201 (50)
Resolved: Non-acute headache at diagnosis and no headache the last year	40/68 (59)	18/33 (55)	12/21 (57)	6/12 (50)	58/101(57)
Improved: Non-acute headache at diagnosis and improvement in experienced headache the last year	16/68 (24)	4/33 (12)	3/21 (14)	1/12(8)	20/101 (20)
Unchanged: Non-acute headache at diagnosis and headache the last year	8/68 (12)	10/33 (30)	5/21 (24)	5/12 (42)	19/101 (18)
Worse: Non-acute headache at diagnosis and worsening in experienced headache the last year	4/68 (6)	1/33 (3)	1/21 (5)	0 (0)	5/101 (5)
New headache: No headache at diagnosis, but headache at follow-up	5/56 (9)	6/44 (14)	3/28 (11)	3/16 (19)	11/100 (11)
Current headache:	33/54	21/54	12/54	9/54	54/201 (27)

*48 of 49 patients had prolactinomas, and 1 patient had a low-grade GH-producing adenoma not operated due to severe comorbidity. †25 of 28 patients had NFA, 1 patient had a low grade acromegaly, and 2 patients with microadenoma and long-term hyperprolactinemia were classified as prolactinomas, but were not treated so far.

TABLE 4. Headache change vs. type of adenoma, n (%)

Type of adenoma	**Non-functional adenomas**			**Functional adenomas**			
	Total	Operated	Non-operated	**Total**	Acromegaly	Mb. Cushing	Prolactinoma
Non-acute headache at diagnosis	53/102 (52)	41/77 (53)	12/25 (48)	48/99 (48)	16/25 (64)	9/21 (43)	23/53 (43)
Resolved	31 (58)	25 (61)	6(50)	27 (56)	8 (50)	6 (67)	13 (57)
Improved	11 (21)	10 (24)	1 (8)	9 (19)	5 (31)	1 (11)	3 (13)
Unchanged	9 (17)	4 (10)	5 (42)	9 (19)	2 (13)	1 (11)	6 (26)
Worse	2 (4)	2 (5)	0	3 (6)	1 (6)	1 (11)	1 (4)
New headache	5/49 (10)	2/36 (6)	3/13 (23)	6/51 (12)	2/9 (22)	1/12 (8)	3/30 (10)
Current headache	27/102	18/77	9/25	27/99	10/25	4/21	13/53

TABLE 5. Sub-classification of current headaches compared to the general population, n (%)

	Operated patients n=124	**Non-operated patients n=77**	**Total n=201**	**HUNT 3 n=39690**
Migraine the last year (self-considered migraine)	4 (3)	4 (5)	8 (4)	3059 (8)
Migraine according to 2010 diagnostic (restrictive) criteria*	4 (3)	10 (13)	14 (7)	4404 (12)
Non-migrainous headache the last year	29 (23)	18 (23)	47 (23)	9329 (24)
Chronic headache >14 days per month	12 (10)	8 (10)	20 (10)	973 (3)

* ICHD-II 2004 [22] except duration of headache, more closely described in reference.