Significant headache improvement after transsphenoidal surgery in patients with small sellar lesions

Clinical article

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Object. Pituitary adenomas represent a large proportion of brain tumors that are increasing in incidence because of improved imaging techniques. Headache is the primary symptom in patients with large tumors (macroadenomas), but is also a symptom in patients with small tumors (microadenomas, tumors < 1.0 cm). The prevalence and optimal treatment of headaches associated with pituitary tumors is still unclear, particularly in cases of microadenoma. If conventional medical management fails, transphenoidal surgery (TSS) may be considered as an alternative treatment for intractable headaches.

Methods. The authors conducted a retrospective review of 512 patients who underwent TSS at Oregon Health & Science University between 2001 and 2007; patients with Cushing disease were excluded. The authors identified 41 patients with small pituitary tumors who underwent TSS, and retrospectively evaluated the resolution and/or treatment of headache.

Results. Ninety percent of patients who presented with nonfunctioning microadenomas and Rathke cleft cysts experienced resolution or improvement in their headaches after TSS, and 56% of patients who presented with hyperfunctioning pituitary microadenomas had improvement in their headaches. There were no postoperative complications.

Conclusions. In this retrospective study, the authors demonstrate the efficacy of TSS in the treatment of intractable headaches in patients who present with pituitary microadenomas (nonsecreting and hypersecretory) and Rathke cleft cysts. (DOI: 10.3171/2008.8.JNS08805)

Key Words • headache • pituitary microadenoma • transphenoidal surgery

The prevalence of headaches associated with brain tumors has previously been reported as 48% for either primary or metastatic tumors. The incidence of pituitary tumors continues to increase, and these lesions now represent the third most common primary or metastatic brain tumor. Headaches are the most commonly reported symptom at presentation (in 33–72% of patients). The reported prevalence of headache in the general population is up to 47% for general headaches, 10% for migraines, 38% for tension-type headaches, and 4–5% for chronic daily headaches. The exact pathophysiology of headaches in pituitary tumors is unknown, however, and is most likely a combination of factors such as compression on vessels and dural structures at the base of the brain, increased sellar pressure, and/or hormonal hypersecretion. Our review of the medical literature provided limited data regarding improvement in pituitary tumor–associated headaches after TSS. The aim of this retrospective study was to assess the efficacy of TSS resection for the treatment of headaches in patients who present with microadenomas (tumors < 1.0 cm) and RCCs.

Methods

We performed a retrospective chart review of 512 patients who underwent TSS between 2001 and 2007 at our institution. Patients with Cushing disease were excluded due to possible confounding factors such as hypercortisolism (endogenous and/or due to treatment with high-dose steroids after the surgery). The study was approved by the Oregon Health & Science University Institutional Review Board. We identified all cases of pituitary microadenomas or RCCs ≤ 1 cm (range 4–10 mm, median...
8 mm) and excluded cases if any dimensions were > 1 cm. Forty-one patients with lesions meeting these criteria were identified, all of whom reported headache as a presenting complaint. All patients underwent follow-up for a minimum of 1 year (median 2 years). The patients were divided into 3 groups for analysis based on tumor pathology: Group 1 comprised all NFAs, Group 2 comprised all identified RCCs, and Group 3 contained all identified GH-secreting tumors and prolactin-secreting tumors. All TSSs were performed by a single neurosurgeon (J.B.D.).

The classification, quality, severity, and location of headache (as reported by the patient) were recorded. Duration and time course (> 2 episodes per week requiring analgesia) were also recorded as part of the patients’ initial primary multidisciplinary consultation. Most patients were referred with an established diagnosis of headache from a neurologist who in some cases discovered the pituitary tumor on MR images. As part of our regular clinical practice, patients also underwent a full evaluation of pituitary function, including low-dose Cortrosyn stimulation test with cortisol measurements, thyroid function (free T4, thyroid-stimulating hormone), insulin growth factor–1, prolactin, luteinizing hormone, follicle-stimulating hormone, and testosterone/estradiol evaluation before and after TSS.

**Results**

The patients in Group 1 were referred to our service following the failure of medical therapy (often multiple regimens) to control chronic headaches. After careful consideration, patients in Groups 1 and 2 opted for tumor resection with the clear understanding that headaches could persist postoperatively. In Group 3, resection was undertaken to cure hormonal hypersecretion. Patients in all groups were ambulatory with no uncontrolled chronic disease or illnesses, and physical and neurological examinations revealed no abnormalities. Chronic daily headaches (as reported by the patients) were predominantly migrainous (in 75%), followed by primary stabbing and cluster headaches. There were no reports of SUNCT.27

Patient clinical and demographic characteristics are outlined in Table 1, and their pre- and postoperative hormonal profiles are shown in Table 2. No additional permanent anterior pituitary deficiencies were observed after TSS.

**Group 1**

Group 1 consisted of 15 patients (3 men and 12 women) with documented NFAs. No patient was on hormone replacement therapy or was receiving medications known to influence prolactin levels or pituitary-thyroidal, adrenal, or gonadal axes. Postoperatively, 8 patients (53.3%) reported complete resolution of headaches, 4 patients (26.6%) reported improvement, and 3 patients (20%) reported no change overall (Fig. 1).

**Group 2**

Group 2 comprised 11 cases (all female patients) with documented RCCs. Transsphenoidal surgery was successful in resolving or improving headaches in 10 patients (completely resolved in 8 and improved in 2). One patient reported no change overall (Fig. 1).

**Group 3**

Group 3 comprised 15 patients (5 male and 10 fe-

**TABLE 2: Summary of pre- and postoperative patient hormonal profiles in all 3 groups**

<table>
<thead>
<tr>
<th>Patient Group</th>
<th>WNL</th>
<th>Hypogonadism</th>
<th>Hypothyroidism</th>
<th>GHD</th>
<th>AI</th>
<th>DI</th>
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<tr>
<td>NFAs preop</td>
<td>10</td>
<td>2</td>
<td>2</td>
<td>0</td>
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<td>0</td>
</tr>
<tr>
<td>postop</td>
<td>7</td>
<td>2</td>
<td>2</td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>RCCs preop</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>postop</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>HFA prolactinomas preop</td>
<td>3</td>
<td>1</td>
<td>0</td>
<td>0</td>
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<td>0</td>
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<tr>
<td>postop</td>
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<td>0</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>GH-secreting tumors preop</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
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<td>5</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
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</tbody>
</table>

* AI = adrenal insufficiency; DI = diabetes insipidus; GHD = growth hormone deficiency; HFA = hyperfunctioning adenoma; WNL = within normal limits.
male patients) with documented hypersecretory microadénomas, including 6 prolactin- and 9 GH-secreting tumors. Transsphenoidal surgery was successful in resolving headaches in 8 patients (53.3%), improving them in 6 patients (40%), and did not result in any improvement in 1 patient (6.6%). Review of prolactinomas compared with GH hypersecretors as diagnosed on pathological examinations revealed that all patients with prolactinomas received headaches benefit, either resolution or reduction, compared with 88.8% of patients with acromegaly (44.4% resolution and 44.4% improvement; Fig. 1).

Accounting for all 41 patients, from the early postoperative period, 85% of patients reported resolution or significant improvement of headache symptoms (Fig. 1). Headaches resolved in 58% of cases, and patients did not require any analgesia during a median follow-up of 2 years. In 29% of patients, headache intensity significantly improved, per subjective recall. In 1 patient, the headaches persisted for 3 weeks postoperatively due to sinusitis after transsphenoidal surgery, which subsequently resolved.

**Discussion**

Headache is the common symptom reported by patients with pituitary adenomas (33–72%), most of which are macroadenomas. The association of headaches with small sellar lesions (nonfunctioning tumors in particular) is not as well-described. The authors of a recent Italian retrospective review of hypersecretory tumors reported that 41.4% of patients presented with headaches, but only 3.4% of these were microadenomas.

In general, migraines are the most frequently reported type of headache in patients with pituitary tumors. In Levy and colleagues’ prospective series, migraine headaches were the most common presentation (in 76% of patients), followed by SUNCT (in 5%), cluster headaches (in 4%), and hemicranias (in 1%). In the present study, chronic daily headaches and self-reported migraines represented 75% of cases, surpassing other types of headaches in all 3 groups. The nonresponsiveness of headaches to standard prophylactic migraine drugs in our sample could represent a selection bias.

The mechanism of headache in pituitary tumors remains unclear. These lesions may provoke headaches directly via a biochemical mechanism, either by eroding laterally into the cavernous sinus containing the first and second divisions of the trigeminal nerve, or by involvement of the dural lining of the sella turcica or diaphragm of the sella also innervated by the trigeminal nerve, or through an increase in intracranial pressure causing dural stretch. Discussions of mechanisms of headaches usually focus on macroadenomas. No association between tumor size or cavernous sinus invasion and headaches has been demonstrated.

Furthermore, Levy et al. emphasized that size and cavernous sinus invasion are not essential in the development of headaches and proposed a new classification to separate pituitary source headaches from hypothalamic disease headaches. Nathoo et al. failed to link pituitary tumor–associated headaches to expression and release of nociceptive substances. Likewise, the role of increased intrasellar pressure remains controversial. Arafah and colleagues demonstrated that intrasellar pressure was higher in patients with pituitary macroadenomas who presented with headaches regardless of tumor size or hypopituitarism status. Other authors were unable to confirm these data. Given that a clear-cut and unified headache mechanism in pituitary macroadenomas has not been postulated, headaches caused by nonfunctioning pituitary microadenomas are even more difficult to explain. Meningeal stretching is an unlikely explanation, and there is usually no cavernous sinus invasion. Evidence

**Fig. 1**. Graph demonstrating significant changes in headache intensity after TSS. HA = headache; PRL = prolactin.
Headache and TSS

for some innate biochemical mechanism is scant. Indeed, it is unknown whether pituitary lesions demonstrated on MR images are responsible for the headaches or whether they should be considered an incidental finding.

Headaches are frequently attributed to the direct effects of the pituitary tumor and hormonal abnormalities that promote vascular headaches. Hormonal abnormalities were carefully excluded as a cause in the NFA and RCC groups (Groups 1 and 2). These groups showed few hormonal deficiencies, and no additional deficiencies or medications were noted postoperatively. The normal hormonal evaluation in our NFA group (Group 1) suggests a structural rather than a neuroendocrine cause of the headaches. Additionally, we were unable to demonstrate a sex difference in headache cure rate. It has been suggested that pituitary tumors may lower the threshold for migraines and that phenotypic family headaches play a role.10,11 Unfortunately a detailed family history of headaches was unavailable for most of our patients.

Headaches associated with RCCs more commonly have characteristic manifestations, a frontal focus with periodicity may indicate an intermittent inflammatory reaction caused by mucous content.26 In a retrospective study of 24 sellar and suprasellar RCCs of variable sizes, headaches at presentation were found in 83% and resolved in 65% of patients after TSS.3 A later study25 showed headache improvement with surgery in 80% of cases. Not surprisingly, headache intensity correlated with high isointense cyst content on MR imaging in this study. Patients with episodic headaches due to RCCs are in general advised to undergo surgical treatment to prevent exacerbation of the inflammation that can result in irreversible endocrine dysfunction. In our RCC group (Group 2) the efficacy of TSS was confirmed with resolution or improvement in 10 (90%) of 11 cases.

The etiology of headaches in hyperfunctioning tumors is not well understood either. Growth hormone–secreting tumors and prolactinomas are considered particularly nociceptive tumors.18,20 To complicate matters, medications used to decrease hormonal hypersecretion can also cause headaches. Medical treatment with DAs could have an unpredictable effect on headaches in microprolactinomas from resolution of migraine after bromocriptine use6 and improvement in postprandial clusterlike headaches with cabergoline use.4,24 However, bromocriptine and other DAs occasionally trigger severe headaches.5,21 In our study, DAs were used in 3 cases with prolactin-secreting tumors (Group 3) prior to surgery with no effect on headaches. We cannot exclude any potential relationship of headaches and cessation of DA after surgery as hyperprolactinemia was normalized in all cases. In our patients with prolactin and GH producing tumors (Group 3), improvement of headaches after TSS correlated with a biochemical cure. Somatostatin analogs are also reported to affect headaches outcomes,15,17 including causing rapid headache improvement in patients with acromegaly that cannot be attributed solely to lowering GH levels,9 and a dramatic benefit in migraines that may produce headache relief via vascular mechanisms.26 Occasionally withdrawal phenomena headaches occur after reduction or discontinuation of octreotide.9 In prolactin and GH hypersecretory tumors, the abolition of headaches with the use of somatostatin analogs and DAs is a well-established option. We report a beneficial effect of TSS in patients with headaches associated with GH- and prolactin-secreting microadenomas (Group 3) that led to biochemical cure of the disease (overall 56% resolution and 40% improvement).

An efficacious management strategy for headaches associated with small pituitary adenomas remains to be determined. Overall in our 41 patients, headaches resolved in 58% with an overall improvement in 85% of patients noted in the early postoperative period (2 weeks to 3 months). Over the 2 years of follow-up, patients reported no analgesic requirement, and 29% reported additional improvement in headaches.

A PubMed database search using the terms “headache” and “transphenoidal surgery” revealed no other studies reporting on outcome of headaches after TSS in patients with small, nonsecreting pituitary microadenomas. Although our results are encouraging, the sample size was small and the data were limited to that of retrospective review. Elucidation of the mechanisms involved in headaches is beyond the scope of this study and at this time it is difficult to determine why headaches completely resolved in some and improved in other patients after TSS. It is possible that our tertiary pituitary center is biased towards more severe headaches associated with pituitary tumors; a possible placebo effect cannot be completely excluded either. We will continue to conduct follow-up in these patients and record their headache experience after TSS.

Conclusions

Despite our excellent results, we do not recommend routine TSS as the initial treatment for headaches associated with small pituitary adenomas and RCCs. However, when patients have severe headaches that are refractory to medical treatment, TSS performed by an experienced pituitary neurosurgeon is a reasonable option. Further prospective studies to confirm these findings are required.

Disclaimer

The authors report no conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.

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