

Pituitary Volume and Headache

Size Is Not Everything

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Background: Pituitary tumors are commonly associated with disabling headache. The accepted mechanisms for headache are dural stretch and cavernous sinus invasion.

Objective: To determine if there is a relationship between pituitary tumor size and the report of headache.

Design: We prospectively studied 63 patients who were initially seen with pituitary tumors. Clinical headache scores, pituitary tumor volume, and the extent of cavernous sinus invasion were obtained for each patient.

Results: The prevalence of headache was 70%. There was no positive correlation the between clinical head-

ache score and pituitary volume ($r = -0.32$, $P = .01$, Spearman rank correlation). There was also no association between cavernous sinus invasion and headache. There was a strong association between pituitary-associated headache and a family history of headache ($\chi^2 = 8.36$, $P = .004$).

Conclusions: These data suggest that a pituitary tumor-associated headache may not simply be a structural problem. Other factors such as family history of headache, and the endocrine activity of the tumor may be equally important determinants of headache. Elucidating these mechanisms will aid in the treatment of these patients and further our understanding of other headache syndromes.

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HEADACHE, A WELL-RECOGNIZED feature of pituitary disease, may be disabling.^{1,2} The reported incidence of headache in pituitary disease ranges with tumor type from 33% to 72% and has been reported to be particularly high in prolactinomas.³ It has long been considered that headache is related to tumor size and dural stretch.^{2,4} The explanation for dural stretch as a cause of headache is that the expansion of a pituitary tumor within the sella turcica stimulates afferent fibers innervating the dura mater, which are certainly known to be pain producing.⁵ Involvement of the cavernous sinus has also been invoked to explain headache³ since the sinus contains the ophthalmic branch of the trigeminal nerve and the internal carotid artery, both of which could generate head pain. However, the mechanical explanation for pituitary tumor-related headache has never been systematically explored, although its implications for management and understanding of the clinical problem are profound.

Headache can be a prominent feature of acromegaly, even with microadenoma,

with approximately 12.5% reporting the symptom.³ Recurrence of headache after treatment may be a clinical sign of further disease activity.⁷ Somatostatin analogues, such as octreotide, can have an immediate analgesic effect in acromegaly-associated headache,⁸⁻¹⁰ in the absence of reduction in tumor size.¹¹ This may be a biochemical effect or a direct effect of activation of somatostatin receptors with antinociceptive effects in the brain.¹²

A variety of headache phenotypes have been associated with pituitary tumors. These include severe and intractable migraine,¹³ trigeminal autonomic cephalgias,¹⁴ such as cluster headache,^{15,16} short-lasting, unilateral neuralgiform headache attacks with conjunctival injection and tearing,^{17,18} and trigeminal neuralgia.¹⁹ In such cases, conventional preventive and abortive headache treatment can often prove to be ineffective, yet medical treatment of the pituitary disease can completely resolve the symptoms. For example, there are reported cases of microprolactinomas manifesting with severe headache that have resolved immediately with the administration of dopamine agonists^{20,21} as well as the impressive analgesic effects of somatostatin

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analogues in acromegaly.^{9,10} However, there are also examples of significant exacerbations of headache with the administration of dopamine-agonists in patients with prolactinomas.^{17,22}

The fact that headache can be dramatically improved or worsened by endocrine treatments, in the absence of any measurable change in pituitary size, suggests that pituitary tumor-associated headache may be a biochemical-neuroendocrine problem rather than a structural one. The aim of this study was to examine systematically the relative importance of size and cavernous sinus invasion in pituitary tumor-associated headache to test directly the hypothesis that local mechanical effects are preeminent in the causation of headache in these patients.

METHODS

Sixty-three patients who were initially seen with pituitary disease were prospectively studied (**Table 1**). All patients were seen in the same unit for treatment of newly diagnosed pituitary disease, which included both surgical and medical management options. Headache, pituitary volume, and cavernous sinus invasion were assessed prospectively with clinical evaluation of headache and structural data being collected by different investigators in a masked fashion.

HEADACHE

Before commencement of treatment, all patients were interviewed by a trained headache fellow or specialist (M.J.L., M.S.M., and P.J.G.). The clinical data collected included the presence or absence of headache and the frequency and severity of symp-

toms. A retrospective clinical headache score covering the period closely related to the magnetic resonance images (MRIs) was calculated using the following formula:

- (1) Headache Frequency (Days per Week)
× Headache Duration (Hours per Day)
× Headache Severity for Peak Attack
(Range, 0 [no pain] to 10 [worst pain imaginable])

To validate this measurement, 22 of the 63 recruited patients (one third of the cohort) were randomly asked to complete prospective headache diaries, in which an hourly headache score was documented for a 2-week period. These diaries were sent to a separate headache specialist, masked to the initial evaluation and the MRI findings, who calculated a mean clinical headache score for each patient. The diary score and the retrospective score were then compared. The presence of a family history of headache was documented in the course of the complete medical history.

PITUITARY VOLUME

The pretreatment MRIs were performed on several different MRI scanners, all at 1.5 T. All examinations included coronal and sagittal T1-weighted spin-echo sequences with a maximum section thickness of 3 mm, before and after intravenous administration of a gadolinium-based contrast medium. All MRIs were assessed by the same neuroradiologist (H.R.J.). For the assessment of the tumor volume, it was assumed that pituitary tumors are ellipsoid.²³ Using Cavalieri's principle, pituitary tumor volume was calculated after performing measurements of tumor diameter in 3 orthogonal planes (**Figure 1A-B**), using the following equation:

$$(2) \quad \text{Volume} = \left[\frac{4}{3} \pi (a/2 \cdot b/2 \cdot c/2) \right]$$

If the tumor was large and multilobed, the tumor volume was assumed to consist of separated ellipsoids and the sum of each lobe volume was calculated (**Figure 1C**).

CAVERNOUS SINUS INVASION

We assessed 3 different parameters for the assessment of presence and degree of cavernous sinus involvement:

1. Encasement of the internal carotid artery, distinguishing 4 grades: no encasement, less than 25% to 50%, more than 50% to 75%, and more than 75% to 100%.
2. Crossing of the 3 lines connecting the cross sections through the distal internal carotid arteries (intercarotid lines): medial, median, and lateral.

Table 1. Clinical Headache Scores* and Tumor Activity

Tumor Subtype	No. of Patients	Female, %	Mean Headache Score
Growth hormone	12	66	758
Prolactin	17	83	659
Thyrotropin	3	66	600
Craniopharyngioma	5	20	362
Nonfunctioning adenoma	20	80	194
Corticotropin	6	100	200

Abbreviation: ACTH, adrenocorticotropic hormone.

*Clinical headache score = headache frequency (days per week) × headache duration (hours per day) × headache severity (range, 0 [none] to 10 [severe]).

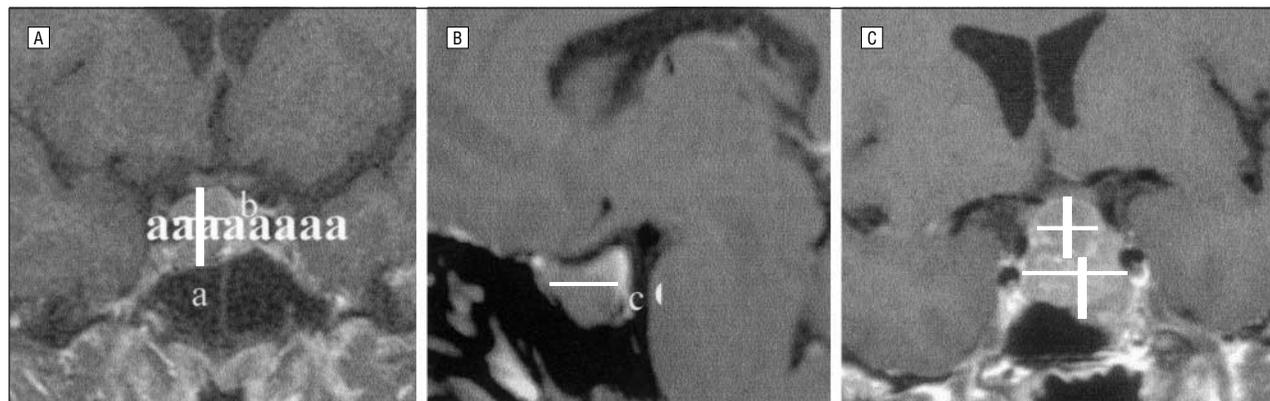


Figure 1. Calculation of pituitary volume for a single-lobed tumor (A and B) and a multilobed tumor (C) assuming the tumor to be ellipsoid. Using 3 orthogonal lines (*a*, *b*, and *c*), $\text{Volume} = \left[\frac{4}{3} \pi (a/2 \cdot b/2 \cdot c/2) \right]$.

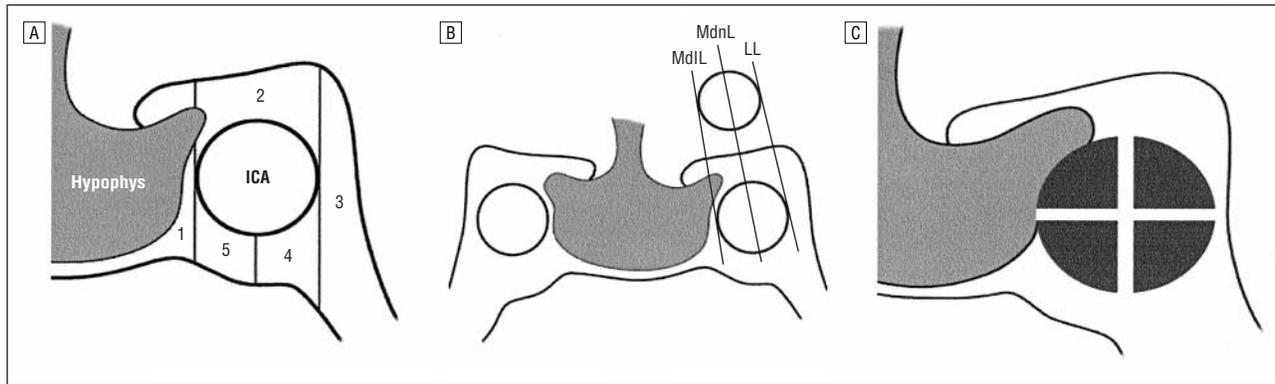


Figure 2. Cavernous sinus invasion. A, The venous compartments are 1, medial; 2, superior; 3, lateral; and 4, carotid sulcus. Hypophysis indicates the pituitary gland; ICA, internal carotid artery. B, The intercarotid lines are medial line (MdL), median line (MdnL), and lateral line (LL). The shaded area is the pituitary gland. C, The carotid artery encasement indicates grade 1, less than 25%; grade 2, more than 25% to 50%; grade 3, more than 50% to 75%; and grade 4, more than 75% to 100%. The shaded area is the pituitary gland. Adapted from Cottier et al.²⁴

3. Extension of the tumor into the venous compartments of the cavernous sinus.

Based on a modification of the classification system described by Cottier et al,²⁴ we distinguished among tumor extension into the superior, lateral, and inferior venous compartments (**Figure 2**). Invasion of the medial compartment had not proved significant in previous studies²⁴ and the inferolateral venous and carotid sulcus compartments were grouped together as the inferior compartment in this study.

Using previously published data comparing MRI classification with surgical findings,^{24,25} we used the following inclusion criteria for cavernous sinus invasion: (1) the tumor crosses the lateral intercarotid line, (2) the tumor encases more than 75% of the internal carotid artery, and (3) the tumor extends into the carotid sulcus venous compartment.

STATISTICS

Nonparametric correlations were used (the Spearman rank correlation) because clinical headache scores were not normally distributed. χ^2 Tests were used to examine associations between cavernous sinus invasion and the presence or absence of headache. Statistical significance was assessed at the $P < .05$ level.

RESULTS

HEADACHE

The prevalence of headache was 70% (44 of 63 patients). The clinical headache scores closely matched the scores obtained from the prospective headache diaries (**Figure 3**; $r = 0.93$, $P < .005$). The highest clinical headache scores were seen in the prolactin- and growth hormone–secreting tumors (Table 1). There was a significant association between pituitary-associated headache and the presence of a family history of headache ($\chi^2 = 8.36$, $P = .004$; **Table 2**).

PITUITARY VOLUME

There was no positive correlation between pituitary volume and headache ($r = -0.32$, $P = .01$; **Figure 4**).

CAVERNOUS SINUS INVASION

There was no association between headache and any compartment of cavernous sinus invasion (Table 2).

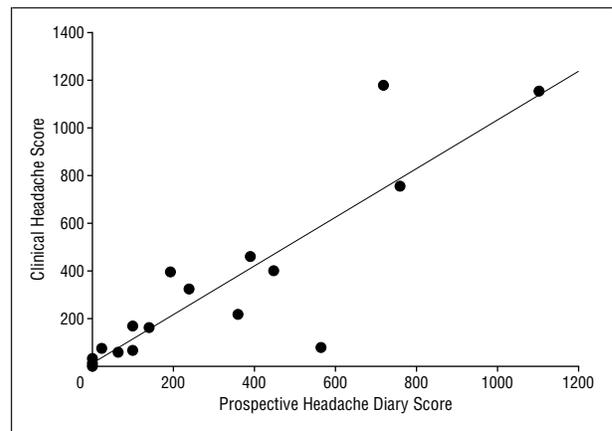


Figure 3. Clinical headache score vs prospective headache diary score. The clinical headache score was calculated as follows: headache frequency (days per week) \times headache duration (hours per day) \times headache severity (range, 0 [none] to 10 [severe]).

Table 2. Cavernous Compartment Sinus Invasion and Family History: Association With Headache

Variable	χ^2 Test	P Value*
Cavernous sinus invasion		
Superior	0.17	>.05
Inferior	0.17	>.05
Lateral	1.08	>.05
Family history of headache	8.36	.004

*Statistical significance was set at $P < .05$.

COMMENT

We found no positive correlation of headache with pituitary tumor volume nor with cavernous sinus invasion, demonstrating that dural stretch and local cavernous sinus invasion are probably not the primary mechanisms behind pituitary tumor-associated headache in most patients. Nevertheless, headache is a frequent and often disabling clinical feature in our cohort and in clinics that treat patients with pituitary tumors. The lack of an association between cavernous sinus in-

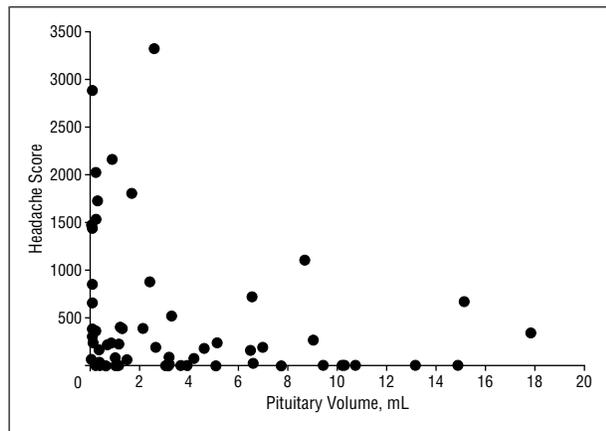


Figure 4. Headache score vs pituitary volume. The clinical headache score was calculated as follows: headache frequency (days per week) \times headache duration (hours per day) \times headache severity (range, 0 [none] to 10 [severe]).

vasion and headache is in agreement with a previous study.³ Our data support a hypothesis that most pituitary tumor-associated headache has a biochemical-neuroendocrine basis and suggest that the pathophysiology of pituitary-related tumor is more complex than may have been considered. However, our clinical experience suggests that there is a subgroup of patients with pituitary tumor-associated headache who have headache and cranial autonomic symptoms ipsilateral to the lesion in whom invasion or some local mechanical effect²⁶ may be important. The latter group of patients seems to be particularly refractory to medical treatment.

The study sought to gain some initial insight into the extent to which the presence of a diagnosed pituitary tumor was associated with headache. Using a clinical headache score can be problematic because interval scale measures are combined with ordinal scale pain scores. However, it does benefit from factoring in the severity of the headache, which for many patients is correlated to the degree of disability they experience. The close correlation between the retrospective clinical headache scores and the prospective headache diaries validates the semiquantitative assessment of headache in these patients with pituitary tumor-associated headache. The headache score concept, as we used it for this study, was motivated by the well-recognized assessment of headache morbidity using MIDAS,²⁷ which uses a similar retrospective approach. These data confirm the clinical impression that these patients have a significant headache problem and was useful in assessing the lack of a systematic role for local structural factors in these patients.

The 70% prevalence of headache in patients with pituitary tumors is significantly higher than the prevalence of headache in the general population.^{28,29} This may represent an ascertainment bias since patients with headache may be more likely to come to care, although it may also be that there is a pronociceptive quality of some pituitary tumors. The latter observation would be consistent with the lack of a significant structural effect for the generation of pain. The preponderance of headache in patients with acromegaly and prolactinoma agrees with our clinical observation that these functional tumors are

particularly pronociceptive. The low clinical headache scores seen in patients with corticotropin-producing adenoma (Cushing disease) is interesting and may relate to the fact that corticosteroids are generally useful in primary headache, albeit without any medium-term or long-term role because of adverse effects.³⁰

Findings from biochemical and animal studies suggest that the hypothalamopituitary axis may play an important role in the pathophysiology of migraine. In migraine there is evidence of hypothalamic dysfunction,³¹ and the presence of polyphagia, polyuria, and polydipsia as part of the premonitory phase of migraine³² further implicates the hypothalamus.³³ The striking relationship between the menstrual cycle and migraine in women suggests that changes in the hypothalamopituitary axis profoundly affect the expression of migraine.^{34,35}

In cluster headache, there is evidence of hypothalamic activation during functional MRI studies,^{36,37} and the circadian rhythmicity further points to the hypothalamus in this disorder.³⁸ Biochemical dysfunction of the hypothalamopituitary axis is well documented in cluster headache.³⁹ Functional imaging studies have also shown hypothalamic activation in patients with short-lasting, unilateral neuralgiform headache attacks with conjunctival hyperemia and tearing,⁴⁰ further suggesting that alteration in hypothalamic function can effect trigeminal pain modulation. Studies of the trigeminohypothalamic tract⁴¹ provide anatomical evidence for a direct neuronal interaction between the hypothalamopituitary axis and the trigeminal nucleus.

The significant association between family history and pituitary tumor-associated headache suggests that genetic factors are important in predicting whether a patient who has a pituitary tumor will develop headache as part of the manifestation. Primary headaches, such as migraine⁴² and cluster headache,⁴³ have a significant genetic predisposition, and the tumor may trigger that predisposition to manifest. The family history data are consistent with a predisposed individual being exposed to a milieu that is pronociceptive and, thus, developing headache.

CONCLUSIONS

It is likely that pituitary tumor-associated headache involves some, yet to be determined, pronociceptive effect of the tumor rather than being due to the structural effects of the tumor itself. Further studies are required to investigate the phenotype of pituitary-associated headache in greater detail and the neuroendocrine mechanisms that are involved, and perhaps differentiate the ultimate expression of the clinical syndromes. This uncommon group of patients may prove to be a useful clinical model to provide insights into the pathophysiology of primary headache more generally. Certainly the new data suggest a reevaluation of the structural hypothesis for the headache associated with pituitary tumors, since it seems likely that these headaches have a more complex pathogenesis.

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