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Expert Opinion

Headache and Pituitary Tumors

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If as Freud wrote, "Neurosis is the inability to tolerate ambiguity," headache specialists must be anything but neurotic. At times it is not clear which abnormalities detected on MRI might cause headache or are instead incidental findings.

CASE 1

A 37-year-old woman was seen with a chief complaint of new onset headaches for 2 months without any prior history of significant headaches. She described a generalized throbbing and aching pain with an intensity of 10/10 associated with light and noise sensitivity and blurred vision in both eyes but no nausea or aura lasting about 3-4 hours with ibuprofen but then recurring requiring another dose of medication. The headaches were occurring about every other day. She was not aware of any triggers. Past medical history was negative. Menses are regular. No history of galactorrhea. Family history was negative for migraine. Neurological examination was normal. Examination by an ophthalmologist including visual fields was normal.

A magnetic resonance imaging (MRI) of the brain and later an MRI of the pituitary with and without contrast revealed a nonhemorrhagic cystic macroadenoma of the left side of the pituitary gland with a small degree of extension to the left suprasellar cistern and displacement into the left side of the sphenoid sinus with remodeling of the floor of the sella turcica abutting but not invading the left cavernous sinus and abutting but not encasing the supraclinoid left internal carotid artery. The adenoma measured 1.3 cm in craniocaudal dimension and 1.1 cm in transverse size with deviation of the infundibulum to the right inferiorly. There was no contact or deformation of the optic chiasm or left optic nerve or tract.

The following blood tests were normal: thyroid stimulating hormone, free T-4, follicle stimulating hormone, luteinizing hormone, prolactin, adrenocorticotrophic hormone, and insulin-like growth factor-I.

CASE 2

A 57-year-old woman presented with a persistent headache. Ten days previously, during orgasm, she suddenly had a severe pressure behind the left eye with an intensity of 10/10 for about 20-30 seconds without any other associated symptoms and then no further headache. Two days prior, she awoke from sleep about 3 AM with the same severe pressure behind the left eye for about 30 seconds. Since then, she has had a constant left-sided pressure behind the left eye and left side of the head with an intensity of 4-5/10 but less today, 2-3/10. There has been light and noise sensitivity, sometimes blurred vision in both eyes but no nausea or other neurological or systemic symptoms. Ibuprofen dulls the pain.

There is no prior history of headaches associated with sex or awakening her from sleep. There is a 10-year history of headaches described as a behind

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the eyes or nuchal-occipital or bifrontal pressure and throbbing with an intensity of 4-5/10 associated with light and noise sensitivity and occasionally nausea but no aura. She would take ibuprofen, lie down and sleep and the headache would resolve in about 2 hours. The headaches were occurring about every 6 months but have not occurred in over 1 year.

Past medical history is negative. Her brother has migraines. Neurological examination was normal. Examination by an ophthalmologist including visual fields was normal.

An MRI of the brain and then an MRI of the pituitary with and without contrast demonstrated a 1.6 in craniocaudal diameter and 1.2 cm in transverse diameter nonenchancing pituitary mass consistent with a macroadenoma within the left side of the pituitary gland resulting in depression of the left side of the sella turcica floor and invasion of the left side of the clivus. There was invasion of the left cavernous sinus with circumferential encasement of the cavernous portion of the left internal carotid artery which demonstrated normal signal flow-void. There was no significant extension of the mass into the suprasellar cistern or mass effect upon the optic apparatus.

The following blood tests were normal: thyroid stimulating hormone, free T-4, follicle stimulating hormone, luteinizing hormone, prolactin, adrenocorticotrophic hormone, and insulin-like growth factor-I.

Questions.—Are the headaches in the 2 cases related to the macroadenomas? What types of headaches are associated with pituitary adenomas? What is the pathophysiology? What is the response to treatment?

EXPERT COMMENTARY

The key question here is whether the pituitary lesions demonstrated on MRI are directly responsible for the presenting headache or simply incidental findings. This is clearly important as surgical removal of the lesion will not lead to an improvement in symptoms if the headache is incorrectly assigned to the pituitary tumor. Pituitary "incidentalomas" are not uncommonly found on routine brain imaging, the prevalence of microadenomas (lesions <1 cm diameter) being as high 1 in 10 in some series.[1] However, incidentally found macroadenomas such as in these 2 cases are less common, with prevalence figures approaching 1 in 500.[2] Case 1 presents with new onset headache and although there are some migrainous features, there is no previous or family history of migraine. Case 2 presents with a more dramatic presentation of unilateral retro-orbital pain during orgasm and there are persistent unilateral symptoms with migrainous exacerbations. In both cases the pituitary lesions are nonfunctioning adenomas.

In the largest prospective series studying headache and pituitary tumors, the most common presentation was migraine (76%) with a relatively high prevalence of short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing (SUNCT) (5%), cluster headache (4%), and hemicrania continua (1%) observed compared with the general population.[3] A significant minority of patients (7%) had an unclassifiable headache characterized by a combination of migrainous and trigeminal autonomic features. Currently, such patients are grouped together in Section 7.4.4 of the International Headache Society diagnostic criteria under the heading "Headache attributed to hypothalamic or pituitary hyper- or hyposecretion."

The pathophysiology of pituitary tumor-associated headache is unknown but may be related to dural stretch, invasion of the cavernous sinus, or functional disturbance within the hypothalamo-pituitary axis. The only 2 studies looking at the relationship between physical properties of pituitary tumors and headache have shown no association between pituitary size or cavernous sinus invasion with headache,[4,5] which is surprising given the presence of the trigeminal nerve within the cavernous sinus and the rich trigeminal innervation of the dura in the sella region. It is well documented that acromegaly associated headache can be aborted with somatostatin analogues,[6] perhaps via the inhibition of some local nociceptive peptide,[7] which raises the question of a biochemical cause of headache in some pituitary tumors. Pituitary apoplexy, during which there is an acute vascular event within a pituitary tumor, presents with acute severe headache, often in association with cranial nerve palsies, visual disturbance, and reduced conscious level. Typically the headache and visual features resolve after surgical treatment.

The appropriate treatment of pituitary tumor-associated headache must be individualized to each case presentation. In patients who present with severe or atypical headache concurrently with other symptoms attributable to pituitary disease, it is reasonable to assume that headache is related to the pituitary pathology. There are several reports of severe new onset refractory cluster headache and SUNCT responding immediately to surgical removal of pituitary tumor or treatment with somatostatin analogues.[8-10] Prolactinomas are more complex, and while treatment with dopamine agonists may abort headache,[11] there are also reports of dramatic exacerbations with bromocriptine and cabergoline, particularly in patients with SUNCT.[12,13]

For those patients where it is unclear if the headache is related to pituitary disease, it is reasonable to treat the headache on its own merits and observe the pharmacological response. In the absence of chiasmal compression or endocrine hypersecretion, many endocrinologists would be comfortable observing a nonfunctioning pituitary adenoma to ensure no growth in the lesion or change in endocrine activity. However, if symptoms of disabling headache persist despite optimal management, then removal of the pituitary lesion might be considered. In Case 1, there is no immediate threat to vision and no endocrine dysfunction and it might be reasonable to treat with migraine prophylactic agents and ensure the lesion does not change in size with a repeat pituitary MRI in several months. If there is no response of headache, then there might be a case for surgery. It would be important to tell the patient that the main indications for surgery are to prevent potential future encroachment of the chiasm and hypopituitarism rather than for the headache alone as symptoms may persist postoperatively.

In Case 2, the sudden onset of headache with orgasm and the ipsilateral cavernous sinus invasion is more suggestive of a direct etiological link between headache and pituitary tumor despite the previous and family history of migraine. There is no mention of high attenuation within the pituitary lesion on MRI although the history raises the possibility of a small bleed within the pituitary lesion. The persistent unilateral pain with migrainous exacerbations after the initial episode raises the possibility of hemicrania continua and a trial of high dose indomethacin would be worthwhile to see if it aborts the headache. If there was no improvement with indomethacin, then transphenoidal surgery would be reasonable given the cavernous sinus invasion and encasement of the internal carotid artery. It is highly likely that residual pituitary tissue would be left postoperatively and further management will depend on symptoms and radiological appearance. Further options include external beam or stereotactic radiotherapy and there is recent evidence that dopamine agonist treatment may prevent the regrowth of residual nonfunctional pituitary lesions.[14]

In summary, the undesirable situation is for patients to have undergone surgery for headache and to experience no improvement in symptoms postoperatively. It is therefore important that there is sufficient indication other than headache to remove a pituitary lesion, which usually relates to size or biochemical properties of the tumor. In the case of functional pituitary lesions such as in acromegaly, persistent postoperative headache may well suggest residual disease requiring further treatment. In nonfunctioning adenomas, if there is no pressing reason to treat the pituitary lesion, then it is reasonable to make an IHS diagnosis and see if headache symptoms resolve with prophylactic treatment, advising against overuse of analgesics in the normal way. If headache is particularly severe, atypical, or refractory to treatment, then surgical removal of the pituitary lesion should be considered after frank and open discussion with the patient, on the proviso that there is no guarantee that the headache will resolve after surgery.

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