A triad of cluster-like headaches with delayed development of a macroscopic prolactinoma: A case report

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Abstract
Pituitary hormone testing is recommended in refractory cluster headache (CH), but supporting evidence is limited. We present a patient with cluster-like headaches and a negative brain magnetic resonance imaging (MRI) 1 year after headache onset. He failed multiple medication trials. Three years after headache onset, additional workup showed abnormal pituitary labs including hyperprolactinemia and a brain MRI with a $15 \times 15 \times 14$ mm³ enhancing pituitary lesion. With cabergoline 0.25 mg twice weekly, the patient has been headache-free for over 2 years. This case supports the recommendations for pituitary testing in refractory CH, even if imaging is initially negative for a pituitary tumor.

Keywords
cluster headache, cabergoline, hypothalamus, pituitary, prolactinoma

Introduction
Pituitary adenomas have a prevalence rate of approximately 0.05–0.1%, with prolactinomas being the most common functioning adenoma.¹ A variety of headache types can arise from pituitary tumors, including migraine, primary stabbing headache, and trigeminal autonomic cephalalgias, such as cluster headache (CH), hemicrania continua, and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing.²,³ Like pituitary adenomas, CH also has a prevalence of approximately 0.1%.⁴ CH is characterized by severe or very severe unilateral attacks of the orbital, supraorbital, or temporal regions that last 15–180 min, occurs with a frequency ranging from once every day up to eight times a day, and is associated with at least one of the following signs and symptoms: ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhea, eyelid edema, forehead and facialhidrosis, miosis, ptosis, restlessness, or agitation.⁵ Recommended workup for CH patients includes a brain magnetic resonance imaging (MRI) with dedicated views of the pituitary and cavernous sinus in all cases; for refractory cases, additional workup includes a magnetic resonance angiogram (MRA) head and neck, imaging of the lung apex, pituitary function testing, and a polysomnogram.⁶ While a limited number of case reports have shown a connection between pituitary tumors and cluster-like headaches,⁷–¹⁴ it is not clear to what extent pituitary testing is useful in refractory CH, especially in patients with a negative pituitary MRI. Here, we present a patient with normal imaging 1 year after headache onset who developed a macroprolactinoma 3 years later.

Case report
Patient presentation
A 35-year-old man with a history of mild traumatic brain injury in 2012 and avascular necrosis of the left hip of

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unclear etiology diagnosed in 2012 was referred for three types of headaches, which began in 2012–2013: mild, moderate, and severe. A timeline of the patient’s clinical course is shown in Figure 1. The mild headaches were holocephalic with mild intensity, no associated symptoms, occurred 2–4 days/week, and were treated effectively with ibuprofen. The moderate headaches were a sharp pain of moderate intensity, centered on the right ear with radiation to the jaw and temple, lasting 4–6 h and occurring one to two times a week without any headache-free months. Associated features included ipsilateral conjunctival injection and right neck stiffness. These headaches invariably occurred the day after the severe headaches but also occurred on other days. The severe headaches were an intense pain limited to the right temporal region (rarely occurring on the left side). Initially, they occurred every Sunday at variable times throughout the day but changed to one to two times a month without any headache-free months. Each attack lasted 10–60 min and was associated with ipsilateral conjunctival injection, ipsilateral rhinorrhea, ipsilateral lacrimation, bilateral photophobia, bilateral phonophobia, and restlessness. These headaches were triggered 1–4 h after drinking alcohol and soon after exercise. He had a long-standing history of headaches similar to the mild headaches, described as holocephalic mild pain that felt like tension, with no associated factors, resolving quickly with acetaminophen, which occurred less than once per week. Neurological examination was normal at all visits with the exception of tenderness along the trapezius that was suggestive of muscular pain.

**Diagnostic assessment and trials**

A brain MRI without contrast in May 2014 was unremarkable, and the patient trialed various treatments between 2014 and 2017 through multiple providers.

**Abortive therapy.** The intensity of his moderate and severe headaches was significantly reduced with multiple abortives, including oxygen, subcutaneous sumatriptan, and intranasal zolmitriptan. His mild headaches responded to ibuprofen and topical lidocaine cream.

**Preventive therapy.** Indomethacin 75 mg three times daily for 2 weeks had no effect on his headaches, suggesting that the patient did not have hemicrania continua or paroxysmal hemicrania. Verapamil and topiramate caused intolerable side effects (constipation and cognitive issues, respectively) and could not be fully uptitrated; they were unhelpful at lower doses. Corticosteroids (oral or suboccipital injections) were not trialed because of his history of avascular necrosis of the hip. The patient had no response to melatonin 12 mg and a slight decrease in frequency with gabapentin 600 mg three times daily. Trigger point injections into the right trapezius and cervical paraspinal muscles gave him 4 weeks of relief of his “mild” headaches in two of four injections that were performed.

**Definitive therapy.** Having done his own research and noting a decreased libido, the patient inquired about lab testing. Testosterone was low at 89 ng/dL (normal: 241–827 ng/dL), and prolactin was elevated at 447.5 ng/mL (normal: 2–18 ng/mL).
Subsequent brain/pituitary MRI with and without contrast revealed an enhancing pituitary lesion consistent with a macroadenoma (Figure 2).

He was initially treated with transdermal testosterone, which was stopped in favor of 0.25 mg cabergoline twice a week. His prolactin level normalized, and 4 weeks after starting cabergoline, he was entirely pain-free and has remained so for over 2 years, with the exception of very rare mild headaches similar to the ones that he had prior to 2012.

**Discussion**

We present an unusual case of a patient with three headaches types—two having many features of CH yet all atypical for CH—which resolved completely with cabergoline. Our patient’s mild headaches were most consistent with tension-type headache, given the holocephalic distribution and lack of associated features. His moderate headaches met some of the International Classification of Headache Disorders third edition (ICHD3) criteria for CH including pain located near the temple and cranial autonomic features (ipsilateral conjunctival injection) but did not meet criteria for pain intensity (moderate instead of severe/very severe), duration (4–6 h instead of 15–180 min), or frequency (one to two times per week instead of between every other day and eight per day). His severe headaches met most ICHD3 criteria for CH (severe pain, temporal location, ipsilateral cranial autonomic features, and falling within the 15–180 min duration period) but were less frequent (only one to four times per month). While he did have a traumatic brain injury within a year of symptom onset, we propose that his prolactinoma is the cause of his headaches, given the resolution of all headaches and normalization of his prolactin level following cabergoline treatment. His case meets all ICHD3 criteria for headache attributed to pituitary hypersecretion (ICHD3 7.4.3), given the headache, demonstration of a pituitary adenoma with hyperprolactinemia, improvement in the headache with improvement in hyperprolactinemia, and an abnormal emotional state (decreased libido). It should be noted that he did not have evidence of a prolactinoma on a brain MRI 1 year after symptom onset but pituitary labs were not performed at that time, so we suspect that the patient had a microscopic functioning adenoma that later grew.

Multiple mechanisms have been proposed for pituitary adenomas causing CH-like attacks, including tumor invasion into adjacent areas, mass effect/tumor size, mass effect/tumor size, hormonal secretion, and inflammation or irritation of pain-sensitive structures, such as the meninges. In our case and one other, CH-like attacks were initially associated with normal imaging that

| Hormone       | Value before treatment (with headaches) | Value after treatment (when headache-free) | Normal range |
|---------------|----------------------------------------|------------------------------------------|--------------|
| Testosterone  | 89                                     | 218                                      | 241–827      |
| Prolactin     | 447.5                                  | 15.3                                     | 2–18         |
| TSH (mIU/L)   | 0.914                                  | 1.69                                     | 0.4–4.5      |
| FSH (mIU/L)   | 1.1                                    | —                                        | 1.6–8        |
| Luteinizing hormone (mIU/L) | 2                                  | —                                        | 1.5–9.3      |
| Estradiol (pg/mL) | 21                                 | —                                        | <39          |

TSH: thyroid-stimulating hormone; FSH: follicle-stimulating hormone.

*Hormone changes accompanying remission of all of the patient’s headaches. The intervention was cabergoline 0.25 mg twice per week.
later revealed a macroadenoma. Unlike our case, the other report was of a single type of headache with typical features of CH. These cases support hormonal secretion as a mechanism of CH-like headaches and argue against tumor invasion or mass effect. Additionally, increased prolactin has been linked to pain via modulation of sensory trigeminal neurons, stimulation of pain pathways, and activation of pain receptors. Nevertheless, other case reports argue the opposite: a nonfunctioning pituitary adenoma has also been implicated in CH, and another case of prolactinoma treated with cabergoline resulted in normalization of prolactin but no change in the CH-like headaches, yet surgical excision resulted in complete remission. These latter cases suggest that excision of select functioning and nonfunctioning pituitary adenomas can result in the resolution of headaches. Yet, given the conflicting data, it is evident that the relationship between pituitary tumors and headaches remains unclear, and headaches alone are a rare indication for surgical management.

Since headaches linked to pituitary adenomas can mimic primary headache disorders, particularly the trigeminal autonomic cephalalgias, it is important to maintain a high index of clinical suspicion for a secondary process in a patient with refractory headaches. If imaging fails to reveal an abnormality, there is benefit in a hormone panel and medical management with alternative pharmacotherapy than usually prescribed for headache.

**Clinical implications**

- Our case suggests that pituitary function testing should be considered in the workup of patients with unusual CH features as well as in those with refractory headaches. Negative brain imaging is insufficient as it does not rule out a microadenoma.

- Our findings add support to current recommendations for workup in CH: a brain MRI in all CH patients, followed by additional testing in refractory cases with MRA head and neck, imaging of the lung apex, pituitary function testing, and a polysomnogram.

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**Informed consent**

Written permission was obtained from the patient for publication of this case report.

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