

Treatment of Severe Trigeminal Headache in Patients With Pituitary Adenomas

Tiago da Silva Freitas, MD*
 Ivan Coelho Ferreira, MD*
 Aldo Pereira Neto, MD, PhD*
 Oswaldo R.M. Neto, MD*
 Gustavo do Vale Gomes, MD§
 Luis Augusto Casulari
 Roxo da Mota, MD, PhD‡
 Luciana Ansaneli Naves, MD,
 PhD‡
 Monalisa F. Azevedo, MD,
 PhD‡

Departments of *Neurosurgery and ‡Endocrinology, University Hospital of Brasília, Brasília, Brazil; §Radiology Department, Hospital Santa Lúcia, Brasília, Brazil

Correspondence:

Tiago da Silva Freitas, MD,
 Departamento de Neurocirurgia,
 Faculdade de Medicina,
 Universidade de Brasília,
 SGAN Quadra 605,
 Asa Norte,
 Prédio Novo de Ambulatórios,
 70840-901 Brasília DF, Brazil.
 E-mail: tmosca@gmail.com

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BACKGROUND: The incidence of headache in patients with pituitary adenomas is high, and the underlying pathological mechanisms are not completely understood.

OBJECTIVE: We tested the efficacy of percutaneous ganglion block and trigeminal rhizotomy in the treatment of severe trigeminal/autonomic headache associated with pituitary tumors.

METHODS: Eleven patients treated surgically for pituitary adenomas in whom intractable trigeminal headaches developed were enrolled in the study and underwent ictal cerebral single-photon emission computed tomography before starting treatment. Initially, all patients underwent a 6-month medical treatment trial. Patients who did not experience improvement in headache severity, addressed by the Headache Impact Test-6 scale, underwent trigeminal percutaneous ganglion blockade. Two patients subsequently underwent trigeminal balloon rhizotomy.

RESULTS: Among the 11 patients, 6 did not have improved Headache Impact Test-6 scale scores after 6 months of treatment with medications and underwent trigeminal ganglion blockade. Significant improvement in headache severity was noted in 3 of them. Long-term response was obtained in 1 patient, and the other 2, in whom the response was transient, were then successfully treated with trigeminal rhizotomy. Cerebral single-photon emission computed tomography showed increased uptake in the thalamus/hypothalamus region in patients who responded well to manipulation of the trigeminal-hypothalamic system.

CONCLUSION: Percutaneous ganglion blockade and trigeminal rhizotomy may be promising alternative options for the treatment of severe headache in selected patients with pituitary adenomas.

KEY WORDS: Autonomic headache, Ganglion block, Pituitary tumor, Trigeminal rhizotomy

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Headache is a common presenting feature of pituitary tumors, and the incidence of this symptom in pituitary adenomas ranges from 33% to 72%.¹⁻³ A variety of headache phenotypes is reported to be associated with pituitary tumors, including migraine⁴ and also the trigeminal autonomic cephalalgias, which comprise cluster headache (severe unilateral pain accompanied by restlessness or agitation and cranial autonomic symptoms); short-lasting, unilateral, neuralgiform headache attacks

with conjunctival injection and tearing; and paroxysmal hemicranias.⁴⁻¹⁰ Migraine, the most common form of headache associated with pituitary adenomas, is a common disabling trigeminal headache disorder, defined as moderate or severe recurring headache, usually unilateral, accompanied by phono/photophobia, nausea, or vomiting.¹¹

The underlying mechanism for the headache in the context of pituitary tumors has long been thought to be mechanical, eg, stretching of the dura mater in the presence of suprasellar extension of the tumor, and/or invasion of the cavernous sinus with trigeminal nerve irritation.^{1,12} However, some patients with huge pituitary tumors with suprasellar extension and

ABBREVIATIONS: HIT-6, Headache Impact Test-6; SPECT, single-photon emission computed tomography

cavernous sinus invasion do not report pain, whereas others present with severe headache associated with relatively small lesions.^{13,14} The fact that headache can be either dramatically improved or worsened by endocrine treatments with somatostatin analogs or dopamine agonists, even in the absence of any measurable change in pituitary size,^{5,15} suggests that pituitary tumor-associated headache may also have a biochemical-neuroendocrine origin. Although some candidate peptides have been demonstrated in pituitary adenomas,^{16,17} no association with headache was found, and the etiology of cephalalgias associated with pituitary lesions remains to be determined.

The treatment of pituitary tumor-associated headache remains entirely empirical because of the lack of trials in this area, which is not unexpected given the rarity of the disease and heterogeneity of the presentation.¹⁸ Generally, the first approach for these patients is the treatment of the tumor, if the lesion warrants treatment on its own merit. Although the indication for treating the pituitary tumor is not headache per se, a number of patients experience improvement in this symptom after surgical or medical treatment of the pituitary lesion.^{19,20}

Nevertheless, a subgroup of patients with trigeminal/autonomic headache present with refractory pain after surgery and/or medical treatment, even with the use of various prophylactic and abortive analgesic medications. In a previous study⁴ and also in our experience at the Endocrinology Unit of the University Hospital of Brasilia (unpublished data), the analgesic effect of somatostatin analogs was observed in some patients with growth hormone-secreting adenomas. However, it was noted that some of them experienced rebound phenomenon and dependency, discouraging the routine use of these agents in the treatment of acromegaly-associated headache.

We describe an alternative approach to patients presenting with pituitary tumors that evolve with severe and intractable trigeminal headache after pituitary surgery.

PATIENTS AND METHODS

Patients and Classification of the Headache

Among the 345 consecutive patients who underwent pituitary surgery at the University Hospital of Brasilia from 1998 to 2007, 20 presented with persistent headache and were referred to the Clinic of Functional Neurosurgery for evaluation. These patients underwent a semiological analysis of their headache (Table 1), and classification of their symptoms was based on the International Headache Society Classification.¹¹ Patients with a diagnosis of persistent headache with a trigeminal/autonomic pattern ($n = 11$) were selected to undergo further analysis. All but 1 patient were hormonally controlled, and the study was conducted from 2007 to 2008.

The severity of headache in these patients was addressed using the Headache Impact Test-6 (HIT-6)²¹ (Table 1). This scale consists of 6 items that evaluate social functioning, pain intensity, and emotional impact of headache as well as well-being, cognitive function, and vitality of the individuals. According to the score in each subclass, the headache is graded as small (≤ 49 points), moderate (50-55 points), substantial (56-59 points), or severe (≥ 60 points). The HIT-6 score was translated

to more than 27 languages, including Brazilian Portuguese, and this instrument of evaluation has been shown to correlate across different diagnostic groups of headache with both headache severity and quality of life.²²⁻²⁴

The study protocol was approved by the Research Ethics Committee of the University of Brasilia, Brazil, and written informed consent was obtained. HIT-6 scale classification of the patients was performed 2 months before starting the protocol treatment twice monthly and 3 and 6 months after clinical and surgical treatment at a frequency of twice monthly. For the analysis, we considered the medium-range results on the HIT-6 scale during the pretreatment period and the medium-range results on the HIT-6 scale during the follow-up.

Cerebral Single-Photon Emission Computed Tomography (SPECT)

The 11 patients involved in the study were submitted to functional analysis with cerebral SPECT in the pretreatment period using the GE Millennium MG—Multi-geometry digital CSE dual-detector gamma camera (General Electric, Milwaukee, Wisconsin). The radionuclide used was technetium 99m-ethylene cysteinate dimer at a dose of 30 mCi intravenously, and we used a high-resolution collimator with a 15% window at 140 KeV. Acquisition started 60 minutes after radionuclide administration, with a resolution of 64×64 pixels and 1.5 zoom.

In the supine position, the patient's head was fixed with a strap so that the brain was fully visible in the inferior portion of the field. We used a circular orbit, 360-degree projections, and 64 frames of 30-second acquisition. The reconstruction type used at the image processing was the iterative method and the attenuation correction was the Chang Order method.

In the SPECT images, which are tomographic images reconstructed in 3 planes (coronal, sagittal, and transaxial) representing the encephalic parenchyma blood flow, the radionuclide was administered intravenously, passed through the blood-brain barrier, and concentrated in the brain according to the perfusion of each site. In the color scale used (GE cool), darker tones meant decreased perfusion and whiter tones meant increased perfusion. In all patients, the examination was performed during an episode of intense headache (ictal SPECT).

Study Protocol

The study protocol included the following. Medical treatment with different medications routinely was used to treat trigeminal/autonomic headaches for a period of 6 months. The impact of the treatment on the relief of headache was determined by the HIT-6 scale score. Improvement of at least 1 level in this scale was considered relevant, and patients who experienced benefit with this approach ($n = 5$) were kept only on medical treatment and were not considered eligible for surgical treatment. The 6 patients who did not experience headache control with medical treatment underwent additional interventional procedures.

Interventional Procedures

The intervention treatment consisted of 2 stages. In the first stage, we performed percutaneous trigeminal ganglion blockade, with the aim of modulating the trigeminal-hypothalamus system possibly involved in the genesis and symptoms of headache in these patients. A series of 3 consecutive blocks using a 2-mL solution containing 120 μ g clonidine and 1 mL of 1% bupivacaine was administered using the

TABLE 1. Protocol Used for the Semiological Analysis of the Headache in the Patients (A) and the Headache Impact Test-6 Scale Parameters (B)^a

A. Semiological Analysis

1. Identification:
Name: Age: Sex:

2. Headache semiology:

2.1 Headache character: pulsatile () heavy weight () shocklike () burning () other _____

2.2. Localization: unilateral () bilateral ()
2.2.2. Frontoparietal () temporal () occipital ()

2.3. Intensity: VAS: _____ HIT-6: _____

2.4. Frequency: _____

2.5. Autonomic phenomenon: conjunctival () nasal block () tear drop ()

2.6. Other symptoms: visual aura () sensitive aura () nausea () photophobia () phonophobia ()

2.7. Time of the symptom: _____

3. Lesion characteristics: Histology: _____ microadenoma () macroadenoma ()

4. Treatment:

4.1. Medications: beta-blocker () tricyclic antidepressants () anticonvulsants () calcium channel blocker () corticosteroid () lithium ()
Other _____

4.2. Medications in pain crisis: _____

4.3. Surgical procedures: Gasser ganglion block () Balloon compression ()

5. Response

	1 month	3 months	6 months
HIT-6			
VAS			

6. Radiological examinations: Ictal SPECT:

B. Headache Impact Test-6

1. Pain intensity: When you have headaches, how often is the pain severe?
Never () Rarely () Sometimes () Very often () Always ()

2. Social functioning: How often do headaches limit your ability to do usual daily activities including household work, work, school, or social activities?
Never () Rarely () Sometimes () Very often () Always ()

3. Well-being: When you have a headache, how often do you wish you could lie down?
Never () Rarely () Sometimes () Very often () Always ()

4. Vitality: In the past 4 weeks, how often have you felt too tired to do work or daily activities because of your headaches?
Never () Rarely () Sometimes () Very often () Always ()

5. Emotional impact: In the past 4 weeks, how often have you felt fed up or irritated because of your headaches? Never () Rarely () Sometimes () Very often () Always ()

6. Cognitive function: In the past 4 weeks, how often did headaches limit your ability to concentrate on work or daily activities? Never () Rarely () Sometimes () Very often () Always ()

(6 points) + (8 points) + (10 points) + (11 points) + (13 points)

Classification:

a) Small (≤49 points)
b) Moderate (50-55 points)
c) Substantial (56-59 points)
d) Severe (≥60 points)

^aVAS, Visual Analog Scale; HIT-6, Headache Impact Test-6; SPECT, single-photon emission computed tomography.

TABLE 2. Characteristics of the 11 Patients Enrolled in the Study^a

Patient	Sex, y/Age	Pattern of Autonomic Headache	Headache Main Symptom at Diagnosis of Pituitary Tumor	Tumor Size Before Pituitary Surgery	Histology	Treatment
1	M/28	Migraine-like	Yes	Macroadenoma	Nonfunctioning	Surgery
2	F/38	Cluster	Yes	Microadenoma	GH	Surgery/somatostatin analog ^d
3	F/41	Cluster	No	Macroadenoma	GH	Surgery/somatostatin analog ^e
4	F/29	Migraine-like	Yes	Microadenoma	Prolactin	Dopamine agonist ^f
5	F/26	Migraine-like	Yes	Macroadenoma	Prolactin	Dopamine agonist/surgery ^g
6	F/28	No class	No	Macroadenoma	GH	Surgery/radiotherapy/ somatostatin analog ^h
7	M/39	Trigeminal neuralgia	Yes	Macroadenoma	Prolactin	Dopamine agonist/surgery ⁱ
8	F/52	Migraine-like	Yes	Macroadenoma	Prolactin	Dopamine agonist/surgery ^j
9	F/45	Cluster	No	Macroadenoma	Nonfunctioning	Surgery
10	M/45	Cluster	No	Microadenoma	GH	Surgery/somatostatin analog ^k
11	F/34	No class	Yes	Macroadenoma	Prolactin	Dopamine agonist/surgery ^l

Patient	Cerebral Ictal SPECT Showing an Increased Uptake in Thalamic-Hypothalamic Region	HIT-6 Scale Score		Percutaneous Ganglion Block	HIT-6 Scale Score ^p		Trigeminal Rhizotomy	HIT-6 Scale Score ^c
		Before Medical Treatment	After Medical Treatment		After 3 mo	After 6 mo		
1	No	58	58	Yes	50	50	No	—
2	Yes	62	62	Yes	62	62	No	—
3	Yes	58	58	Yes	50	58	Yes	48
4	No	50	44	No	—	—	No	—
5	No	52	46	No	—	—	No	—
6	No	70	70	Yes	70	70	No	—
7	No	48	42	No	—	—	No	—
8	No	51	46	No	—	—	No	—
9	Yes	58	58	Yes	50	58	Yes	46
10	Yes	54	46	No	—	—	No	—
11	No	73	73	Yes	73	73	No	—

^aPatients who did not respond to medical treatment subsequently underwent interventional procedures. HIT-6 score: 40 to 49, small; 50 to 55, moderate; 56 to 59, substantial; more than 59, severe. SPECT, single-photon emission computed tomography; HIT-6, Headache Impact Test-6; GH, growth hormone; IGF-I, insulinlike growth factor I.

^bHIT-6 score determined after the interventional treatment: 3 and 6 months after percutaneous ganglion block intervention.

^cHIT-6 score determined after the interventional treatment: 3 months after trigeminal rhizotomy.

^{d-l}Hormonal levels when the patient was enrolled in the study.

^dIGF-I 595 ng/mL (normal range, 106-277).

^eIGF-I 92 ng/mL (normal range, 98-261).

^fProlactin 19.3 ng/mL (normal range, 0.33-27.33).^gProlactin 10.4 ng/mL (normal range, 0.33-27.33).

^hIGF-I 174 ng/mL (normal range, 117-321).

ⁱProlactin 22 (normal range, 0.33-27.33).

^jProlactin 12 ng/mL (normal range, 0.33-27.33).

^kIGF-I 110 ng/mL (normal range, 98- 261).

^lProlactin 17 (normal range, 0.33-27.33).

percutaneous Härtel technique, traditionally used to treat trigeminal neuralgias²⁵ (Figure 1).

Two patients who showed transitory pain relief with the percutaneous trigeminal ganglion blockade underwent the second stage of the surgical treatment: trigeminal percutaneous rhizotomy with a balloon, which was performed in the operating room with the aid of fluoroscopic imaging. Light general anesthesia was induced, and then an external pacemaker was placed on the patient's chest to set the depressor response. Pre-operative atropine was not given so that the depressor response could be used as a parameter of trigeminal compression.

Patients were positioned supine, with a roll under their shoulders, allowing approximately 20 degrees of extension. A 14-gauge introducing cannula was percutaneously passed to the foramen using Härtel guidelines and aided by lateral fluoroscopic imaging. Often a brief trigeminal depressor response occurs from mechanical compression of the mandibular nerve at the foramen. Once the cannula had engaged the foramen ovale, the blunt obturator was removed and a straight guiding stylet inserted. Using the anteroposterior image (with the petrous ridge positioned in the radiographic center of the orbit), the stylet was directed at the medial dip in the petrous bone, which is the proximal entrance to

TABLE 3. Medium-Range Results on Headache Impact Test-6 Scale Determined Throughout the Study^a

HIT-6 Scale Topics	Pretreatment Period											After Conservative Treatment										
Patient	1	2	3	4	5	6	7	8	9	10	11	1	2	3	4	5	6	7	8	9	10	11
Pain intensity	13	11	11	10	10	13	8	11	13	11	11	13	11	11	6	8	13	6	11	13	8	11
Social functioning	11	13	13	8	10	11	8	8	11	11	13	11	13	13	6	6	11	6	8	11	6	13
Well-being	8	10	8	8	10	11	8	8	8	8	13	8	10	8	8	10	11	6	8	8	8	13
Vitality	10	10	10	10	8	11	8	8	8	8	10	10	10	10	10	8	11	8	8	8	8	10
Emotional impact	8	10	8	6	8	13	8	8	10	8	13	8	10	8	6	8	13	8	8	10	8	13
Cognitive functioning	8	8	8	8	6	11	8	8	8	8	13	8	8	8	8	6	11	8	8	8	8	13
Final HIT-6 scale score	58	62	58	50	52	70	48	51	58	54	73	58	62	58	44	46	70	42	46	58	46	73

HIT-6 Scale Topics	After Percutaneous Gasser Ganglion Block											After Balloon		
Patient	1	2	3	6	9	11	3	9						
Follow-up, mo	3	6	3	6	3	6	3	6	3	6	3	6	3	3
Pain intensity	8	8	11	11	8	11	13	13	10	13	11	11	8	10
Social functioning	10	10	13	13	10	13	11	11	8	11	13	13	10	8
Well-being	8	8	10	10	8	8	11	11	8	8	13	13	8	8
Vitality	10	10	10	10	10	10	11	11	8	8	10	10	8	6
Emotional impact	6	6	10	10	6	8	13	13	8	10	13	13	6	6
Cognitive functioning	8	8	8	8	8	8	11	11	8	8	13	13	8	8
Final HIT-6 scale score	50	50	62	62	50	58	70	70	50	58	73	73	48	46

^aHIT-6, Headache Impact Test-6. HIT-6 scale score: 40 to 49, small; 50 to 55, moderate; 56 to 59, substantial; more than 59, severe.

the Meckel cave, the porus trigeminus, found approximately 17 mm beyond the foramen ovale. The tip of the stylet was set approximately 2 mm beyond the edge of the petrous ridge as seen through the orbit. Once properly positioned, the stylet was withdrawn and the balloon catheter inserted into the same site.

The lateral view of the cranium was used during the balloon compression. Air was evacuated from the balloon with a tuberculin syringe connected to a 3-way stopcock. The balloon was inflated with 0.7 to 0.75 mL of 180 mg% iohexol, and once a corresponding pear shape was observed, the balloon was left inflated for 1 to 1.5 minutes. The pear shape indicates that the tip of the balloon lies within the porus trigeminus, which is where it must lie to compress the trigeminal nerve adequately.

The depressor response was observed in both patients at this point, briefly triggering the external pacemaker. Intermittent lateral imaging was obtained to monitor the balloon's position and shape. The needle and catheter were then removed, and sterile bandage applied to the cheek. Both patients were discharged the following morning.

RESULTS

The characteristics of the 11 patients with trigeminal/autonomic headache are shown in Table 2. Four patients had growth hormone-secreting adenomas; all but 1 (patient 2) were under endocrine control after surgery and with the use of somatostatin analog. Another 4 patients with prolactinomas were initially treated with dopamine agonists and were cured after pituitary surgery. One patient with microprolactinoma was treated only with dopamine agonist. The other 2 patients had nonfunctioning

pituitary adenomas. In 8 of the 11 patients, headache was the main symptom at the time of diagnosis of pituitary adenoma.

All individuals enrolled had their headache severity quantified by the HIT-6 scale, as detailed in Table 3, and functionally studied through cerebral SPECT performed during an ictal period. All but 1 patient (number 7) had their headache classified as, at least, moderate, and 3 of them had severe headache, by the HIT-6 scale. As shown in Figure 2, cerebral SPECT showed increased uptake in the peri-insular/insular and thalamic/hypothalamic regions in the 4 patients who presented with trigeminal/autonomic headache of a cluster-like pattern (patients 2, 3, 9, and 10). The other 7 patients had their trigeminal/autonomic headache subclassified as migraine-like (patients 1, 4, 5, and 8), trigeminal neuralgia (patient 7), and “no class” (patients 6 and 11), and none of them showed the same alterations in the cerebral SPECT (Figure 3).

All patients were initially submitted to medical treatment, and the intensity of the headaches was readdressed after 6 months. Three patients with migraine-like pain and one with cluster-like symptoms presented a significant decrease in scoring in the HIT-6 scale classification, changing their headache status from moderate to small (Table 2). These 4 patients together with the patient with trigeminal neuralgia, who experienced a 6-point decrease in the HIT-6 scale score, were kept on medical treatment with no further procedures because the benefit of the conservative approach was considered evident and relevant. Medications used, side effects, and final doses for each patient are shown in Table 4.

TABLE 4. Clinical Treatment: Medications, Side Effects, and Doses Used During the Study Protocol^a

Patient	Medications Prescribed	Side Effects	Final Medications and Final Doses
1	AMT, PRO, TOP, VAL	VAL: nausea, drowsiness	AMT: 75 mg/d PRO: 120 mg/d TOP: 75 mg/d
2	LIT, VAL, VER	None	LIT: 1200 mg/d VAL: 1000 mg/d VER: 240 mg/d
3	LIT, VAL, VER	VER: water retention, drowsiness	LIT: 1200 mg/d
4	NTP, TOP	None	VAL: 1000 mg/d NTP: 50 mg/d TOP: 75 mg/d
5	AMT, PRO	None	AMT: 75 mg/d PRO: 160 mg/d
6	AMT, TOP, VAL, VEN, VER	VAL: nausea, drowsiness VEN: nausea	AMT: 75 mg/d TOP: 100 mg/d VER: 240 mg/d
7	CBZ, TOP	None	CBZ: 1000 mg/d TOP: 50 mg/d
8	AMT, PRO, VAL	None	AMT: 50 mg/d PRO: 120 mg/d VAL: 1000 mg/d
9	LIT, VAL, VER	None	LIT: 1800 mg/d VAL: 1000 mg/d VER: 360 mg/d
10	VAL, VER	None	VAL: 1000 mg/d VER: 480 mg/d
11	AMT, VAL, PRO, TOP	None	AMT: 75 mg/d VAL: 1000 mg/d PRO: 120 mg/d TOP: 75 mg/d

^aAMT, amitriptyline; PRO, propranolol; TOP, topiramate; VAL, valproic acid; LIT, lithium carbonate; VER, verapamil; NTP, nortriptyline; VEN, venlafaxine; CBZ, carbamazepine.

The other 6 patients who did not experience improvement in headache after 6 months of medical treatment underwent percutaneous trigeminal ganglion blockade. One patient with migraine-like pain (patient 1) had his headache classification changed from substantial to moderate after 3 and 6 months of follow-up (Table 2). One patient with cluster headache (patient 2, the only patient who was not hormonally controlled when enrolled in the study) and 2 patients with an unclassified pattern (patients 6 and 11) did not experience any benefit as shown by the HIT-6 scale score after the percutaneous ganglion blockade and did not undergo any additional procedures. Patients 3 and 9, presenting with cluster headache, showed an initial response to treatment, with the HIT-6 scale classification changing from

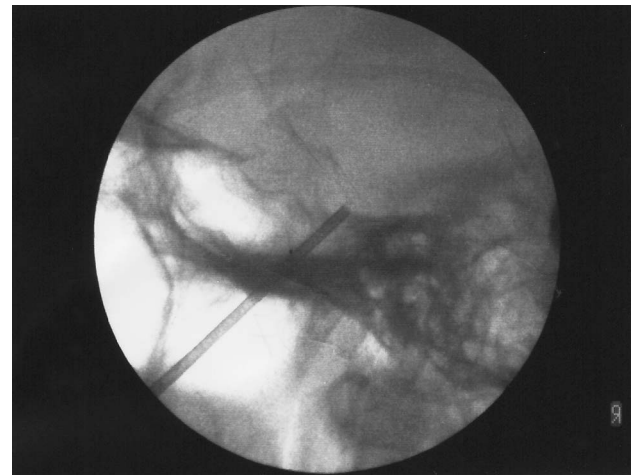


FIGURE 1. Puncture of the ganglion of Gasser guided by radioscopy, performed using the Härtel technique.

substantial to moderate after 4 months. However, this effect was transitory, and the score returned to moderate after 6 months (Table 2).

Based on the initial response to the ganglion blockade, these 2 patients (patients 3 and 9) were assigned for the trigeminal rhizotomy with balloon compression. Three months after the procedure, significant changes in the HIT-6 scale score were noted. In both patients, the headache was reclassified from substantial to small, according to the HIT-6 scale score (Table 2). The benefit was also maintained after more than 1 year of follow-up (data not shown).

No complications related to the interventional procedures (percutaneous trigeminal ganglion blockade and trigeminal rhizotomy with balloon compression) were observed in any patient involved in the study.

DISCUSSION

Although headache has long been recognized as a common symptom associated with pituitary lesions,¹⁻³ the pathophysiology of pituitary tumor-related cephalalgias is still unknown. Dural stretch and invasion of the cavernous sinus explain many, but not all, cases of headache in this setting. The hypothesis of a biochemical cause has been postulated to justify the pain in a subgroup of patients with pituitary tumors that respond to somatostatin analogs, perhaps via the inhibition of some local nociceptive peptide,²⁰ but a definite mechanism is still to be established.

Pituitary adenomas require an intervention, eg, surgical removal or treatment with somatostatin analogs (for growth hormone-secreting adenomas) or dopamine agonists (for prolactinomas)

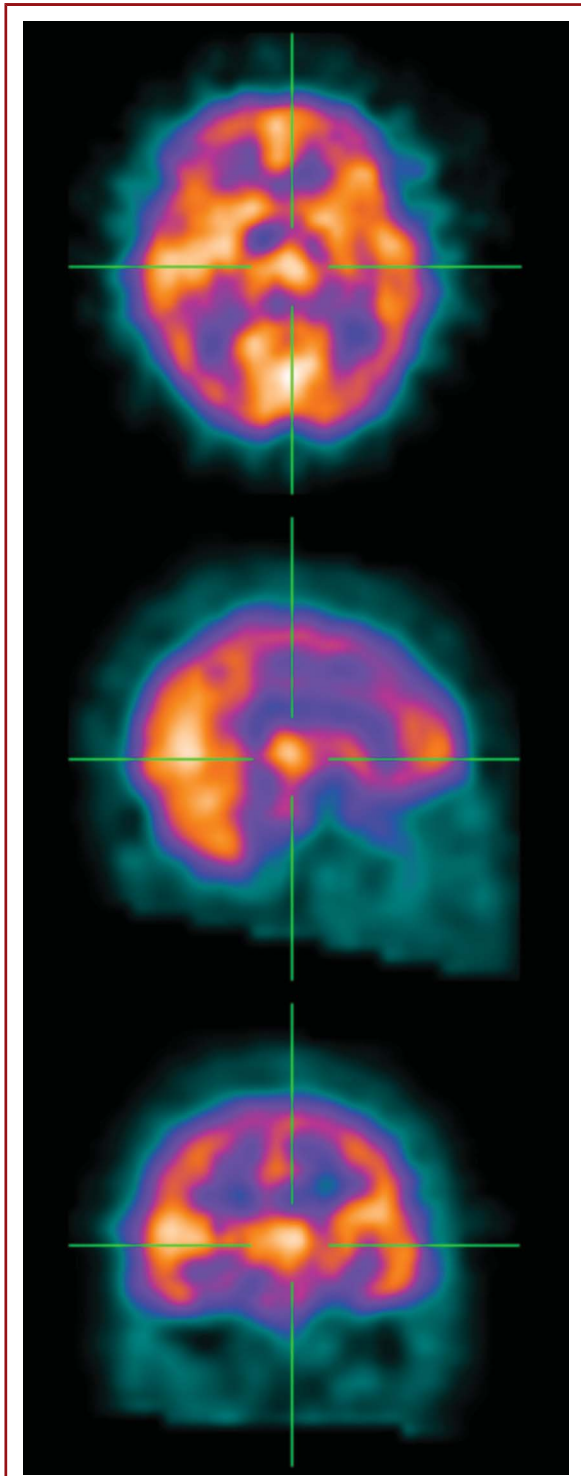


FIGURE 2. Cerebral ictal single-photon emission computed tomography (SPECT) performed in patient 2, showing increased uptake in the thalamic/hypothalamic region, bilaterally. Patients 3, 9, and 10 also presented a similar pattern on the SPECT scan.

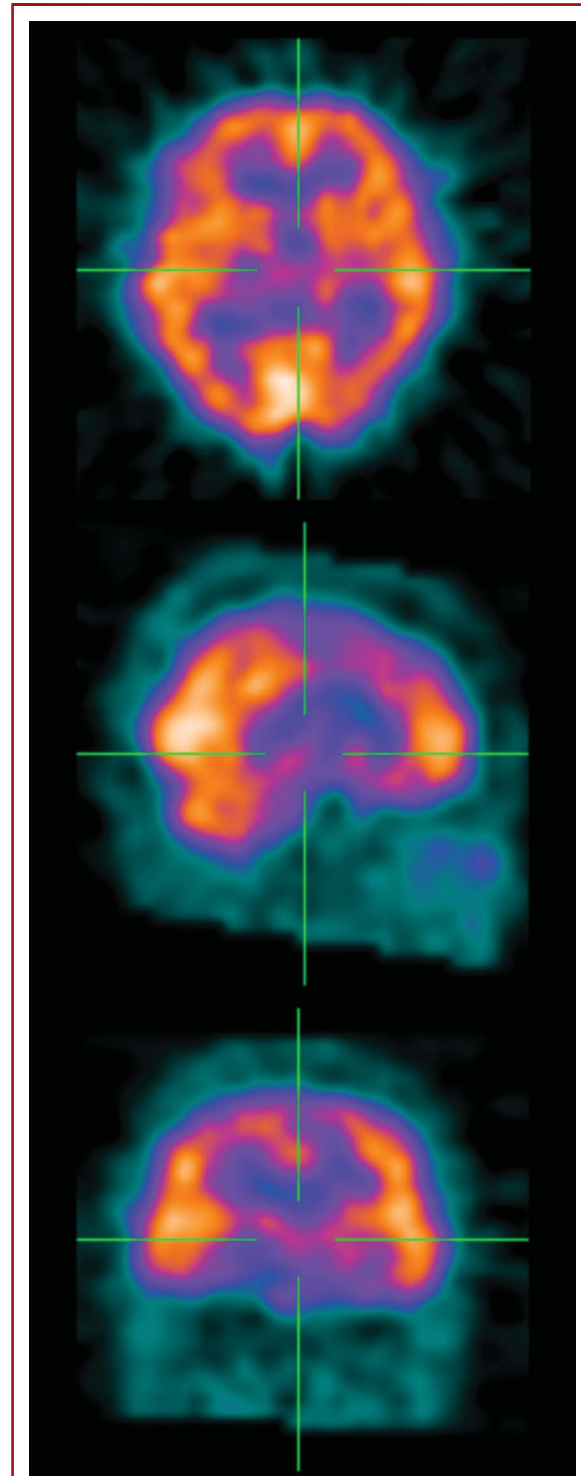


FIGURE 3. Cerebral ictal single-photon emission computed tomography performed in patient 1. Note the absence of increased uptake in the thalamic/hypothalamic region. The same pattern was observed in patients 4, 5, 6, 7, 8, and 11.

when any threat to the optic chiasm or endocrine hypersecretion is observed.²⁶⁻²⁹ Headache may be aborted with the pituitary tumor approach, although this is not a rule nor is the presence of headache an indication for treatment.

After surgical removal of the pituitary tumor, a minority of patients evolve with persistent and severe headache, most of the time with an autonomic pattern, which is resistant to conservative treatments such as tricyclic antidepressants, anticonvulsants, beta-blockers, calcium channel blockers, dopamine agonists, and corticosteroids.^{6,14,30} Some of these patients obtain relief with subcutaneous injections of somatostatin analogs, but our experience shows that these patients become addicted to the drug; they require progressively higher doses of the medication, with loss of the analgesic effect, thus discouraging this approach as a routine. In this study, 8 of the 11 patients with persistent headache after surgery had this symptom as the main manifestation at the time of diagnosis of pituitary adenoma. All patients were kept on medical treatment throughout the study, regardless of the interventional procedures to which they were assigned, and our main goal was to investigate alternative approaches that could provide pain relief in this setting.

To our knowledge, this is the first time that percutaneous Gasser ganglion block and trigeminal percutaneous rhizotomy were used for the treatment of trigeminal/autonomic headache associated with pituitary tumors. Although the placebo effect cannot be ruled out in this study, according to our results, the interventional procedures may be promising options for the treatment of such patients, in addition to conventional medical treatment. The effectiveness of percutaneous Gasser ganglion block was observed in 1 patient with migraine-like headache, whereas a transitory benefit was seen in 2 patients with cluster autonomic headache.

Moreover, based on previous reports in the literature of the successful use of trigeminal rhizotomy in patients with primary cluster headache,³¹⁻³³ we performed this surgical technique in the 2 patients with cluster headache who presented a previous transitory response to percutaneous ganglion block. A significant and sustained improvement in the pain intensity was observed in both after rhizotomy, suggesting that this procedure may be an alternative for the treatment of cluster headache in the context of pituitary adenomas.

In an effort to better define the trigeminal pattern of headache in our patients, we performed functional studies with cerebral SPECT during the ictal period. In 4 of the 11 patients, an increased uptake of the contrast was observed in the peri-insular/insular and thalamic/hypothalamic regions, suggesting a possible role for reduced blood flow in this area in the underlying mechanism for the headache. Previous studies of cerebral blood flow in trigeminal headaches, using SPECT, are few in number, and the results have been heterogeneous.³⁴⁻³⁸ In the most recent study, a reduced cerebral blood flow was observed in the thalamus region in patients with cluster headache compared with healthy volunteers.³⁹ In this study, the alterations were seen outside the active period of headache.³⁹

In our study, the 4 patients who presented altered cerebral blood flow in SPECT had cluster headache, and 1 of them was successfully treated with trigeminal ganglion blockade, whereas 2 others who presented a transitory response to this procedure were successfully treated with percutaneous rhizotomy. These findings may suggest a relationship between the thalamic/hypothalamic pattern on SPECT and the response to surgical procedures. Unfortunately, it was not possible to perform the SPECT during a headache-free period, which limits our conclusions about the utility of this modality of functional study in the approach of the headache associated with pituitary adenomas.

Our study, performed in a small number of patients, represents the first insight for a potential benefit of percutaneous Gasser ganglion block and percutaneous balloon compression (trigeminal rhizotomy) in the treatment of severe trigeminal/autonomic headache associated with pituitary tumors.

Disclosure

The authors have no personal financial or institutional interest in any of the drugs, materials, or drugs described in this article.

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COMMENTS

The pathomechanisms of pituitary adenoma associated facial pain is still unsolved. The authors present a series of 11 patients (3.2%) out of a total of 345 patients who still had untractable trigeminal headaches persisting after pituitary adenoma surgery. Unfortunately there are no data on the remaining 96.8% of patients according to their pre- and postoperative status regarding headaches. Among the 11 investigated patients, medical treatment had no significant effect in 6 patients, so that these were treated by percutaneous ganglion block and/or additional trigeminal rhizotomy, reducing the pain in 3 of them. This study illustrates that pituitary adenoma associated pain is a definite challenge that necessitates a sophisticated therapeutic strategy in selected cases.

Hopefully, further insight in the pathophysiological mechanism will offer additional treatment options in the future.

Christopher Nimsky
Marburg, Germany

The authors evaluated their experience in managing medically intractable headaches in a small subset of patients after removal of pituitary tumors. Several of these patients had growth hormone-secreting tumors, which can notoriously cause headaches even after surgical cure or hormonal control of insulinlike growth factor I with somatostatin analogs. The authors classified 11 of these patients as having trigeminal headaches of a presumed autonomic origin. They provide single-photon emission computed tomography data to suggest involvement of the hypothalamic region in mediating the control of these headaches and document improvement in headache symptoms after trigeminal blockade or rhizotomy in 3 patients.

Although this is a very nice effort to classify an unusual headache syndrome and provide a treatment rationale, I am left with many questions and uncertainties. Headache is extremely common in patients with pituitary tumors, and almost 75% will report improvement in symptoms after surgery. However, not all patients with headaches and pituitary tumors have their symptoms relieved by surgery. Headache is one of the most common medical disorders known, and it is quite reasonable that the subset of patients described here had headaches that had nothing to do with their pituitary tumor. Also, of note, these patients did not have trigeminal neuralgia, but rather trigeminal headache. Unilateral rhizotomy or trigeminal blockade was effective in reducing headache in 3 of 6 patients treated, but even these patients were not completely cured of symptoms. A similar efficacy may be seen in headache sufferers without pituitary tumors. Further, placebo effect may play a large role because it often does in headache sufferers. Placebo effects can account for up to 40% of response to any treatment for headache. Unfortunately, this article does not really provide the practitioner any new guidelines for treatment or a clear way to determine who might benefit from this invasive and potentially risky treatment. It may suggest further lines of headache research, but I do not believe that the current data are compelling enough to recommend trigeminal blockade in patients with intractable headaches, and I would not suggest such treatment for my patients based on this report. Nonetheless, I laud the efforts of the authors in collecting and reporting these data and provoking further inquiry into the nature of these debilitating headaches.

Adam N. Mamelak
Los Angeles, California

The authors present their experience gleaned from 345 patients with pituitary adenoma. However, details of only a few patients were presented. Criteria for selecting those patients are not clear nor are the details of symptoms of the majority of the patients presented. In how many of the entire group was pituitary adenoma discovered during evaluation for headache? Consequently, this cannot be considered a study of the entire population of patients seen by the authors, but rather case histories of the patients, presumably randomly selected, that are presented in detail. Because there was no consistent response to management, no firm conclusions or recommendations for treatment have emerged. However, the experience demonstrates how difficult it can be to manage headache that persists after treatment of pituitary adenoma.

Philip L. Gildenberg
Houston, Texas