

# Cerebral Vasospasm Following Transsphenoidal Hypophysectomy in the Treatment of Lymphocytic Hypophysitis

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**Abstract:** Cerebral vasospasm following transsphenoidal hypophysectomy is an exceedingly rare but serious complication with high morbidity and mortality. The initial signs and symptoms of cerebral vasospasm following transsphenoidal hypophysectomy are changes in mental status, motor deficits, and speech difficulties. Symptomatic vasospasm is difficult to reverse despite treatment and often only resolves with time. Furthermore, most transsphenoidal hypophysectomy patients have been discharged before the onset of vasospasm, so when they do present it is often in a fulminant form and recalcitrant to available treatments.

All previously reported patients of cerebral vasospasm following transsphenoidal hypophysectomy were status postresection of a pituitary macroadenoma. The authors report the first patient of vasospasm following transsphenoidal hypophysectomy in the treatment of lymphocytic hypophysitis; a rare inflammatory disorder characterized by lymphocytic infiltration of the pituitary gland causing destruction glandular tissue.

**Key Words:** Delayed cerebral ischemia, lymphocytic hypophysitis, transsphenoidal, vasospasm

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Cerebral vasospasm (CV) is a well-recognized cause of morbidity following aneurysmal subarachnoid hemorrhage. Less commonly, it has been reported to occur after tumor surgery particularly those involving the skull base with proximity to large caliber cerebral vasculature. The clinical course of vasospasm in this setting parallels that of the postsubarachnoid hemorrhage patient and typically peaks 5 to 10 days after the event. However, because this entity is rare in the setting of tumor resection, patients are typically not monitored for its occurrence nor treated prophylactically for its prevention. They often present to the hospital with a fulminant form that is difficult to treat. With the increased popularity and expanding indications for endoscopic endonasal surgery

of the sella and parasellar regions, it is important to recognize this potential complication. There are 11 known patients of CV following transsphenoidal surgery, all associated with the resection of pituitary macroadenomas.<sup>1,2</sup> We report the first patient of vasospasm following transsphenoidal hypophysectomy (TSH) in the treatment of lymphocytic hypophysitis and propose another potential cause of cerebral vasospasm following TSH.

## CLINICAL PRESENTATION

This patient is a 19-year-old right-handed college woman with a medical history of prediabetes who suffered from a 4-year history of vague visual complaints including intermittent tunnel vision. She presented as an emergency room transfer after a 1-month history of worsening intractable nausea, vomiting, vertigo, severe new-onset headaches, fatigue, heat intolerance, muscle aches, and generalized weakness. The patient had a history of menstrual irregularities but was otherwise healthy. She did not have a family history of autoimmune disease. Examination was normal including formal visual field testing that did not show a visual field cut. Hormonal testing was consistent with hypopituitarism, including secondary adrenal insufficiency, secondary hypothyroidism, and central hypogonadism. Prolactin levels were normal and there was no evidence of diabetes insipidus. A magnetic resonance imaging (MRI) revealed a 1.7 cm × 1.6 cm × 1.4 cm peripherally enhancing pituitary mass with suprasellar extension with mass effect upon the optic chiasm (Figs. 1 and 2).

The patient underwent a stereotactic endoscopic transsphenoidal biopsy using a three-handed endonasal approach. Intraoperatively, the lesion was necrotic with a thicker peripheral rind. Frozen section was reported as a pituitary adenoma and further resection proceeded. Careful dissection into the subarachnoid space was performed to identify the stalk and normal pituitary gland for their preservation and to decompress the optic apparatus. Multilayered closure commenced utilizing a nasal septal flap. There was no arterial manipulation or injury and the surgery was otherwise uncomplicated. Intraoperative blood loss was estimated to be 230 mL with little or no bleeding into the subarachnoid space. The patient's visual disturbances resolved postoperatively but her headaches persisted. She underwent hormone replacement for panhypopituitarism and was maintained on prophylactic antibiotics. There was no evidence of postoperative cerebral spinal fluid leak and she was discharged from the hospital on postoperative day 4. Final pathologic analysis of the lesion revealed dense infiltrates of lymphocytes and plasma cells effacing the normal adenohypophysis architecture. Immunohistochemical stains revealed as many as 50 IgG4-positive plasma cells per high-power field. Lymphoid follicles with germinal centers and parenchymal fibrosis were also evident, all findings that are consistent with lymphocytic hypophysitis (LH).

On postoperative day 9, the patient represented with episodic changes in mental status and slurred speech. An MRI/magnetic

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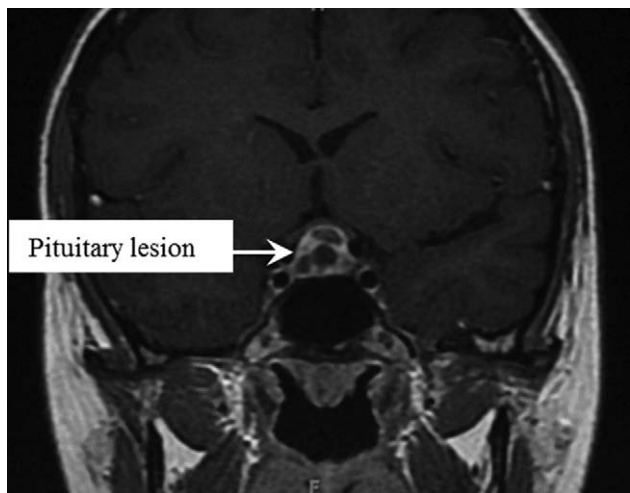
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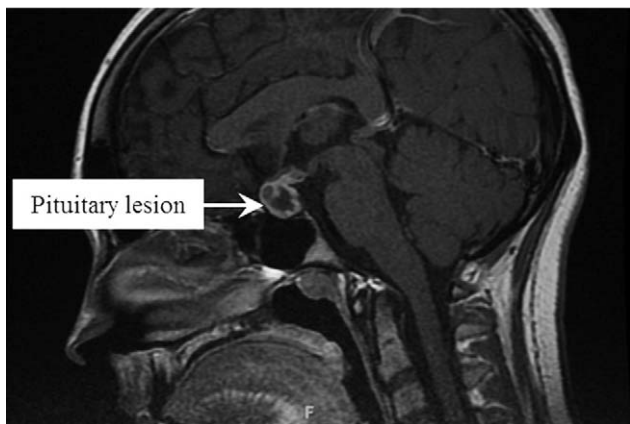
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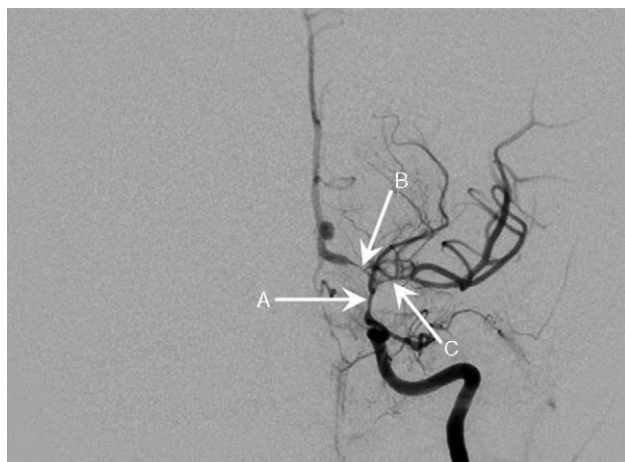


**FIGURE 1.** Preoperative coronal magnetic resonance imaging revealed a 1.7 cm × 1.6 m × 1.4 cm peripherally enhancing pituitary mass with suprasellar extension with mass effect upon the optic chiasm.

resonance angiography of the brain showed a small left basal ganglia infarct and vasospasm of the left supraclinoid internal carotid artery, proximal middle cerebral artery, and anterior cerebral artery segments. The patient was immediately started on intravenous fluids and nimodipine; hypotension was avoided. Despite initial improvement, the next day she developed acute expressive aphasia, episodic right hemiparesis, and became lethargic requiring intubation for airway protection. Emergent catheter angiography was performed which revealed moderate to severe vasospasm involving the left supraclinoid internal carotid artery, M1 middle cerebral artery, and A1 anterior cerebral artery segments with restrictive downstream flow (Fig. 3). She was treated with intra-arterial vasodilators, including Nicardipine several times and a trial of Milrinone, with limited improvement. Ultimately, despite all efforts she went on to develop global aphasia and right hemiplegia. An MRI showed patchy areas of stroke. She ultimately required tracheostomy and gastrostomy placement. At 8 month follow-up she has residual hemiparesis and improving residual expressive aphasia. There are no signs of Wernicke aphasia and she can communicate fully with text messages. She is able to ambulate independently and continues to undergo speech therapy.



**FIGURE 2.** Preoperative sagittal magnetic resonance imaging revealed a 1.7 cm × 1.6 m × 1.4 cm peripherally enhancing pituitary mass with suprasellar extension with mass effect upon the optic chiasm.



**FIGURE 3.** Catheter angiography revealed (A) moderate to severe vasospasm of left supraclinoid internal carotid artery; (B) severe vasospasm involving the proximal A1; and (C) severe vasospasm involving the proximal M1.

### Lymphocytic Hypophysitis

Lymphocytic hypophysitis is a rare inflammatory disorder characterized by lymphocytic infiltration of the pituitary gland with subsequent destruction and fibrosis of glandular tissue.<sup>3–6</sup> Lymphocytic hypophysitis is the most common form of primary hypophysitis. Other less common forms of primary hypophysitis are granulomatous, xanthomatous, and necrotizing hypophysitis. The pathogenesis of LH has been attributed to autoimmunity due to the presence of other autoimmune disorders, such as Hashimoto thyroiditis and Addison disease in one-third of patients.<sup>7,8</sup> Furthermore, although with low sensitivity, antipituitary antibodies have also been detected in patients' serum.<sup>9,10</sup> The disorder most often affects women of childbearing age. It has a strong association with pregnancy as 49% to 57% of women are affected late in pregnancy or in the first 2 months postpartum.<sup>10,11</sup> However, in recent years, there have been increased reports of the disorder manifesting in men (15% of patients), postmenopausal women, and even children.<sup>3,6,11</sup> As of 2013, there have only been 390 published patients of biopsy-proven LH.<sup>10</sup> While the precise incidence is unknown, it has been estimated to be 1 in every 10 million.<sup>4,10,12</sup> Histopathological diagnosis is confirmed with the presence of both T-cell and B-cell lymphocytes infiltrating and surrounding pituitary cells. Infiltrates may also include the presence of plasma cells, eosinophils, macrophages, and neutrophils.<sup>10,11</sup> Lymphocytic hypophysitis can be further classified by location. It most commonly affects the anterior pituitary lobe (adenohypophysitis) but may also involve the posterior lobe and infundibulum (infundibulo-neurohypophysitis) or both lobes (panhypophysitis).<sup>10,13</sup>

The lymphocytic infiltration of the pituitary gland forms a sellar mass that can expand upward and impinge upon the optic chiasm, dura mater, or cavernous sinus.<sup>10</sup> The most common symptoms of LH originate from this mass effect and include generalized headaches and visual disturbances. The remainder of symptoms is a result of pituitary insufficiency.<sup>6,10,11,14</sup> Corticotroph cells are most commonly affected causing general malaise, hypertension, nausea, vomiting, and dizziness. In some patients of LH, particularly if diagnosis and treatment are delayed, acute adrenal crisis can result in the death of the patient. Thyrotroph cells are also commonly affected causing fatigue, lethargy, cold intolerance, and weight gain.<sup>6,10</sup> When LH is suspected, MRI with and without contrast is the diagnostic imaging of choice.<sup>14</sup> Several authors have described MRI features that can help distinguish autoimmune hypophysitis

from other sellar masses, such as stalk diameter, lesion shape symmetry, and signal intensity following contrast. However, none of these features are specific enough to diagnose hypophysitis.<sup>10,14</sup> Given its similar clinical presentation and radiographic findings, LH is often misdiagnosed as a nonfunctioning pituitary adenoma.<sup>3</sup> In 1 series by Leung et al,<sup>4</sup> 38% of patients of primary hypophysitis were initially diagnosed as pituitary macroadenoma and only after pathological evaluation of surgical specimens was the diagnosis correctly made.

Definitive diagnosis of LH can only be made with histological evaluation of tissue following biopsy or surgical resection.<sup>6</sup> In cases where a presumptive diagnosis can be made and in the absence of mass effect, close observation for spontaneous resolution with hormone replacement or treatment with glucocorticoids can be pursued.<sup>11</sup> In the presence of mass effect, continued deterioration despite medical management or the need for definitive diagnosis, surgery should be undertaken.<sup>9</sup> An endoscopic transsphenoidal approach, the surgical technique of choice in recent years, has been proven to be safe and effective.<sup>8,10</sup> The goal of surgery is to debulk the pituitary mass and relieve the compression of cranial nerves and pressure responsible for headaches, while making every effort to preserve normal pituitary tissue.<sup>14</sup>

## DISCUSSION

Pituitary surgery is indicated for several reasons: resection of masses that causes compression effects such as visual disturbances, correction of hormonal hypersecretion from functional tumors, and in some patients, for diagnostic tissue evaluation.<sup>11</sup> The surgical approach to pituitary lesions is either transcranial or transsphenoidal. The first successful transsphenoidal approach was reported by Schloffer in 1907 and has continued to be refined over the years with improvements in techniques and technology, particularly the use of endoscopes.<sup>11</sup> The result has been a significant reduction in morbidity and mortality when compared with craniotomy. Currently, these procedures are often a joint effort by a neurosurgeon and an otolaryngologist via an endonasal approach. Most patients are ambulatory within 6 to 9 hours and are discharged within 3 days postoperatively.<sup>11</sup>

While endonasal transsphenoidal surgery has been proven to be safe and effective, common complications include cerebral spinal fluid leak, diabetes insipidus, hypopituitarism, transient or permanent vision loss, and meningitis.<sup>15</sup> Local damage may also lead to vascular bleeding with hematoma formation or epistaxis.<sup>11</sup> Cerebral vasospasm following transsphenoidal pituitary surgery is a rare but serious complication with high morbidity and mortality.<sup>1,16</sup>

The incidence of CV following subarachnoid hemorrhage is a well-described phenomenon that most frequently occurs following the rupture of a cerebral aneurysm, but may also be associated with infection, inflammation, trauma, and posterior reversible encephalopathy syndrome.<sup>16</sup> Although much less common, we also find reports of CV occurring following the resection of skull based tumors, typically via a transcranial approach.<sup>1</sup> Cerebral vasospasm following a transsphenoidal approach continues to be exceedingly rare. All of the reported patients occurred following resection of pituitary adenomas signifying that CV has never been reported following resection of LH, another very rare disease process.

Like its aneurysmal counterpart, tumor-related CV occurs 5 to 10 days postictus and can last up to 3 weeks. It is associated with increased vessel reactivity, narrowing of the intraluminal vessel diameter, and restriction of blood flow, which can lead to downstream ischemic complications. It can occur in up to 70% of patients and result in delayed ischemic events in 20% to 30%; however, its true incidence is likely higher than recognized.<sup>17,18</sup> In documented patients, the initial signs and symptoms of CV following TSH are

changes in mental status, motor deficits, and speech difficulties.<sup>15</sup> The average time to develop clinical CV following tumor resection is 8 days.<sup>1</sup> Patients have often already been discharged prior to symptom onset, so the clinician needs to have a high level of clinical suspicion if the patient returns to the emergency room with mental status, motor deficits, or speech difficulties. Furthermore, vasospasm has a strong association with cerebral salt wasting, so it is imperative to not presumptuously attribute altered mental status to overcorrection of diabetes insipidus in the hyponatremic post pituitary patient when vasospasm may in fact be the underlying cause.

A variety of strategies have been employed when treating CV following TSH, including “Triple-H” therapy (hypertension, hypervolemia, and hemodilution), use of nimodipine, an L-type voltage gated calcium channel blocker proven to improve treatment outcomes, catheter angiography with infusion of vasodilators and balloon angioplasty to mechanically open the stenosed vessel and “break” the vasospasm cycle.<sup>1,2,15,19</sup> However, symptomatic vasospasm is difficult to reverse despite treatment and often only resolves with time. Furthermore, most tumor patients have been discharged before the onset of vasospasm, so when they do present it is often in a fulminant form and recalcitrant to available treatments. Despite treatment, morbidity and mortality of CV postpituitary surgery remain quite high, reported to be 59% and 28% respectively.<sup>15</sup>

## CONCLUSION

Cerebral vasospasm is a rare complication of transsphenoidal hypophysectomy but carries with it significant morbidity and mortality. Clinicians should have a high level of clinical suspicion for CV when patients develop altered mental status, motor deficits, or speech difficulties following TSH. While all previously reported patients involved resection of pituitary macroadenomas, our study has revealed that this significant complication also occurs with resection of lymphocytic hypophysitis.

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