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Grand Rounds

A 64-year-old woman with dilated right pupil, nausea, and headache

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History

A 64-year-old woman presented with a dilated right pupil and nausea that began 3 days after the onset of a mild but constant headache. She complained of an inability to focus but had no loss of vision and reported no diplopia in primary gaze. There was associated photophobia but no neck stiffness. She had completed 2 weeks of therapeutic enoxaparin for a right below-knee deep vein thrombosis (DVT), diagnosed a month prior. Anticoagulation medication was prescribed after a follow-up scan at 2 weeks showed minimal residual DVT in a branch of the medial gastrocnemius vein along with partial resolution of the thrombus in the greater saphenous vein. The patient's medical history was remarkable for hypothyroidism, but she did not suffer from hypertension, diabetes, or cardiovascular disease. She had noticed a gradual weight gain over the preceding year, and her primary care physician began testing free urinary cortisol 2 weeks prior to presentation.

Examination

On physical examination, she exhibited a cushingoid habitus and centripetal obesity. Vital signs were normal. Best-corrected visual acuity was 6/6 in both eyes. Neuro-ophthalmic assessment revealed a right partial ptosis with a fixed and dilated right pupil measuring 7 mm on the right (no direct or consensual response to light) and a reactive pupil measuring 3 mm on the left. Fundus examination was normal. Ocular motility showed limited adduction, elevation, and depression of the right eye but full ductions of the left eye (Figure 1). There was subjective diplopia on left and up- gazes. Visual fields were intact on confrontation. The remainder of the cranial nerve examination was unremarkable. Formal perimetry confirmed intact visual fields.

Ancillary Testing

Computed tomography (CT) of the head demonstrated an intrasellar mass abutting the optic chiasm, with no evidence of subarachnoid hemorrhage or an unruptured aneurysm on CT angiogram. Magnetic resonance imaging (MRI) of the brain confirmed a pituitary macroadenoma with suprasellar extension and hemorrhage with mass effect and tumor extension into the pituitary infundibulum and cavernous sinuses (Figures 2–3). Endocrine studies showed no evidence of anterior pituitary dysfunction except reduced level of thyroid-stimulating hormone (TSH), suggestive of a response to long-term thyroxine. Urinary cortisol was elevated (272; normal <150 nmol/day).

Treatment

High-dose dexamethasone was administered to avoid Addisonian crisis in consultation with endocrinology. Complete recovery in oculomotor nerve function was noted by day 3 with conservative management only. No further diplopia, headache, or nausea was reported. Transsphenoidal resection was avoided, and the patient made an uneventful recovery after discontinuation of enoxaparin. She was discharged on hydrocortisone and continued thyroxine replacement.

Differential Diagnosis

An ischemic etiology is considered in patients presenting with a pupil-sparing, oculomotor nerve palsy. Such patients should have a complete blood count, including glucose and cholesterol studies.

This patient presented with pupil-involving oculomotor nerve palsy. An important differential that must be considered with pupil involvement is an evolving compressive oculomotor nerve lesion. An urgent angiogram is needed to exclude an aneurysm.

Acute-onset paralysis of the oculomotor nerve has been described as the chief presenting complaint of pituitary apoplexy in only a few cases in the literature.[1] Pituitary

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Digital Journal of Ophthalmology

Figure 1. Photographs showing right oculomotor nerve palsy, with sparing of abducens nerve function (abduction) in right gaze, ptosis and mydriasis of the right eye in primary position, and restricted adduction in left gaze.

Figure 2. T1-weighted magnetic resonance imaging (MRI), sagittal view, showing hyperintense sellar mass (optic chiasm indicated by arrow).

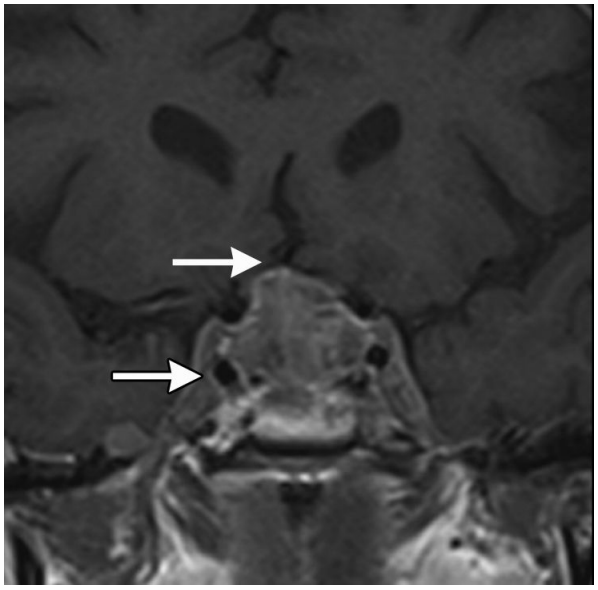

Figure 3. MRI, coronal view, showing gross expansion of pituitary fossa with heterogeneous high T1 signal reflecting blood products. There is infiltration of the cavernous sinuses (outlined arrow) bilaterally with effacement of the undersurface of the optic chiasm (arrow).

apoplexy refers to the clinical syndrome associated with hemorrhagic infarction of a preexisting pituitary adenoma, classically manifesting with the sudden onset of headache, nausea and vomiting, visual impairment (decreased acuity, field deficits, or impaired ocular motility), and altered mental status. The word “apoplexy” is of Greek origin and describes the accumulation of blood or fluid within any organ.[1] Apoplectic events are unpredictable and often misdiagnosed.[2] The presentation may also be complicated by meningism. Delayed diagnosis increases the risk of permanent visual impairment. Successful management of pituitary apoplexy relies on early diagnosis, with appropriate medical management of acute adrenal insufficiency and surgical intervention to optimize visual outcome. The history may have clues to the longstanding presence of a pituitary tumor (headache, visual loss, endocrine problems), with the acute episode manifested by signs of compression by hematoma and pituitary destruction. Pituitary function tests, such as prolactin, thyroid function, and gonadotropins, are also essential to guide further hormonal therapy and confirm the extent of pituitary compromise.

Diagnosis and Discussion

Pituitary apoplexy occurs spontaneously in the majority of cases.[2,3] Factors postulated as predisposing to apoplexy have included head trauma, hypertension, sudden changes in arterial or intracranial pressure, use of bromocriptine, dynamic pituitary function testing, radiotherapy, diabetes, and anticoagulation.[2,4]

A timely diagnosis of pituitary apoplexy of a preexisting pituitary adenoma was made in this case. Pituitary apo-

Table 1. Case report compilation of isolated oculomotor nerve palsies without documented visual field or acuity deficits

Case	Author	Pituitary tumor function	Precipitating factor	Complete/incomplete palsy	Treatment	Interval between ictus and surgery	Recovery
1	De Araujo et al[16]	Nonfunctioning	Head injury	Near complete	Surgery	2.5 months	Complete
2	De Araujo et al[16]	Nonfunctioning	Head injury	Complete	Conservative		Nearly complete
3	Saul and Hilliker[2]	Nonfunctioning	None	Complete	Bromocriptine		Complete
4	Saul and Hilliker[2]	Nonfunctioning	None	Complete	Conservative		Complete
5	Saul and Hilliker[2]	Cushing disease	None	Incomplete	Surgery	10 months	Partial
6	Saul and Hilliker[2]	Nonfunctioning	None	Complete	Surgery	Several days	Complete
7	Rossitch et al[15]	Nonfunctioning	None	Incomplete	Surgery	7 days	Complete
8	Brisman et al[13]	Prolactinoma	None	Complete	Bromocriptine		Complete
9	Chen et al[17]	Unknown	Uncertain	Complete	Surgery	Unknown	Complete
10	Lee et al[18]	Nonfunctioning	None	Complete	Conservative		Complete
11	Lenthall and Jaspan[14]	Prolactinoma	None	Partial	Not mentioned		Not mentioned
12	Varma et al[20]	Nonfunctioning	None	Incomplete	Surgery	2 months	Complete
13	Kashkouli et al[8]	Nonfunctioning	None	Complete	Surgery	10 days	Complete
14	Cho et al[5]	Nonfunctioning	None	Incomplete	Surgery	5 days	Complete
15	Cho et al[5]	Nonfunctioning	Sheehan syndrome	Incomplete	Surgery	3 days	Complete
16	Woo et al[12]	Nonfunctioning	None	Not mentioned	Surgery	15	Complete
17	Kobayashi et al[10]	Nonfunctioning	None	Complete	Surgery	9 days	Complete
18	Kobayashi et al[10]	Nonfunctioning	None	Incomplete	Surgery	5 days	Complete
19	Present study	Cushing disease	Enoxaparin	Partial	Conservative		Complete

plexy is an uncommon and potentially fatal condition. It is a sight-threatening emergency for which a variety of presenting features have been described. Various degrees of cranial nerve palsy can result from compression of cranial nerves III, IV, V, and VI, with an expanding mass in the cavernous sinus.[5] However, isolated oculomotor nerve palsy without visual acuity or field deficits as the presenting sign of pituitary apoplexy is rare (Table 1).

In a retrospective series, Randeva et al (1999)[3] found headache to be the most reliable presenting symptom, followed by nausea and a reduction in visual fields. Additional symptoms include changes in the level of consciousness, meningeal irritation, and ophthalmoplegia.[1] The triad of incomplete eye movements, pupil asymmetry, and ptosis is suggestive of an oculomotor nerve lesion with pupillary dilatation in addition to ptosis being indicative of a mass lesion compressing the oculomotor nerve. Possible compression within the subarachnoid space should also be considered, as with a posterior-communicating arterial aneurysm or a supratentorial mass with impending herniation. Ophthalmic manifestations of pituitary apoplexy arise from superior and/or lateral expansion of the tumor.[6]

The pituitary gland lies in the sella turcica, near the hypothalamus and optic chiasm. It is surrounded by the sphenoid bone and covered by the sellar diaphragm (an extension of the dura). Like the cranial vault, the walls of the sella turcica are normally rigid with sudden and rapid rises in intrasellar pressure resulting from apoplexy. Visual field impairment is common with superior expansion into the optic nerve or chiasm from which a bitemporal defect is classically seen. Formal documentation of any field defects should be obtained at presentation in all stable patients.

The present case demonstrated radiological mass effect on the optic chiasm without any visual acuity or visual field deficits. Cases of oculomotor nerve palsy without visual field defects have been reported and follow a favorable prognosis (Table 1). Diplopia occurs due to compression of the cranial nerves in the cavernous sinus but may be masked by ptosis, obscuring vision in the affected eye in some cases of oculomotor nerve palsy.[7] The oculomotor nerve is the third and largest of the cranial nerves to the extraocular muscles and lies below the optic tract as it pierces the arachnoid and dura matter at the roof of the cavernous sinus. Possible mechanisms of oculomotor nerve palsy from pituitary adenomas include direct compression of the nerve by tumor invasion of the cavernous sinus, transmission of pressure on the cavernous sinus wall by tumor expansion, edematous expansion due to hemorrhage or ischemic infarction of the tumor, direct infiltration of the tumor, and vascular occlusion of the nerve.[8] Because it is more horizontally situated in the cavernous sinus, the oculomotor nerve is susceptible to lateral pressure from an expanding mass compressing it between the tumor and the inter-clinoid ligament.[8,9] Despite being a commonly affected cranial nerve, cases of isolated oculomotor nerve palsy (without visual acuity or field deficits) are rarely described as the initial feature of ophthalmoplegia in pituitary apoplexy, perhaps because of the confluence of other structures within the cavernous sinus, making it unlikely for dam-

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age to the third nerve in this area to present as an isolated palsy.[10]

Although there are a few case series reported[8,11–13] of isolated oculomotor nerve palsy in pituitary apoplexy, most of these cases also included visual field and/or visual acuity deficits. In some cases, visual deficits were not mentioned or cases of isolated oculomotor nerve palsy were not elaborated and hence not included in our review.[8,11] To our knowledge, our study is the only compilation of isolated oculomotor nerve palsy case reports without visual deficits in the literature (Table 1). In total, there were 19 case reports (including the present case), of which the majority were non-functioning pituitary adenomas. In case number 11, there was no mention of treatment or the outcome.[14] Two cases each were of Cushing's disease and prolactinomas.[9,14,15] In the majority of these cases, no precipitating factors were found. The precipitating factors include 2 cases of mild head injury[16] and 1 each of Sheehan's syndrome[5] and anticoagulation (present case). In contrast, Sibal et al[12] found that 40% of pituitary apoplexy cases had a precipitating factor. In complete oculomotor nerve palsies, 5 of each were treated with surgery and conservative treatment, with complete recovery in all cases.[6,9,10,15–18] In incomplete paresis cases, 7 underwent surgery and 1 conservative treatment. [5,9,10,14,19,20] All recovered completely except for 1 case, in which the palsy had been present for 10 months.[9]

Our patient did not require surgery and recovered complete oculomotor nerve function within 3 days of steroid treatment. At follow-up at 1 and 2 months after discharge, sustained resolution of the palsy was noted; formal field testing, repeated after 3 months, was normal. Because there are no randomized trials on pituitary apoplexy cases with cranial neuropathy, there is no evidence in favor of either surgery or conservative treatment. Randeva et al reported improvement in ocular paresis with surgery, with complete recovery of visual acuity in all cases if operated within 8 days and complete recovery in 46% of cases if operated after 8 days. The present case, by contrast, describes isolated ophthalmoplegia without visual acuity or field deficits.[3] Kim et al[8] noted that time to recovery from cranial nerve palsies accompanying pituitary tumors after surgery and the interval between development of symptoms and surgery were positively and significantly correlated. Maccagnan et al[21] and Gruber et al[22] found no evidence that early operative decompression is associated with an improved outcome. Most of the patients managed conservatively had minor visual field and acuity deficits. As indicated in our compilation, pure oculomotor palsies recover well with either conservative or surgical treatment.

The acute onset of isolated oculomotor nerve palsy with pupillary involvement should alert clinicians to the possibility of pituitary apoplexy and the need for urgent angiography to rule out an aneurysm, followed by MRI and early neurosurgical referral. Given the variability of presentation, the importance of recognizing a pituitary tumor as the etiology of isolated third nerve palsy has been emphasized. Pupillary involvement is a crucial diagnostic sign.

In conclusion, this case report emphasizes not only the importance of recognizing pituitary apoplexy as the etiology of isolated oculomotor nerve palsy but also the need for prompt imaging of the undifferentiated endocrine patient before commencing anticoagulation. Early ophthalmoplegia without visual field deficits may be monitored for spontaneous resolution of oculomotor nerve palsy. Conservative treatment can be successful in certain cases of pituitary apoplexy with oculomotor nerve involvement.

Literature Search

A systematic review of the English literature was conducted in 2011 on multiple databases (MEDLINE, PubMed, and EMBASE) for relevant articles from the period 1950–2011. Search terms included *pituitary apoplexy*, *isolated third nerve palsy*, *oculomotor*, and *anticoagulation*. Only articles documenting isolated oculomotor nerve palsies without visual acuity or field deficits were compiled.

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