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## Case Report: The Dilemma of Imaging an Isolated Sixth Nerve Palsy

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## Case Report: The Dilemma of Imaging an Isolated Sixth Nerve Palsy

### Abstract

**Background:** Traditionally, eyecare providers employ a wait-and-see approach with respect to older patients presenting with a presumed vasculopathic isolated sixth nerve palsy. However, given review of recent literature and the potential of morbidity in these patients, acute neuroimaging should be strongly considered. Eyecare providers are often faced with challenging decisions when patients present with acute isolated oculomotor nerve palsies. This case highlights the diagnostic dilemma of an older patient with significant vasculopathic risk factors who presents with an isolated sixth nerve palsy. For patients older than 50, a vasculopathic etiology is the most likely cause, however, a small but significant percentage of these patients may suffer from a more ominous condition such as, giant cell arteritis, intracranial mass, or aneurysm. As evidenced by our case, acute neuro imaging should be considered in all isolated sixth nerve palsies.

**Case Report:** A 69- year old Caucasian male presented to the VA Connecticut Healthcare System with new onset diplopia. The patient reported a recent history of mild orbital pain and headaches. Evaluation revealed an isolated left sixth nerve palsy. A microvascular etiology was presumed given his strong vasculopathic history. One week later the patient returned to clinic with a new left pupil-sparing third nerve palsy in addition to his original left sixth nerve palsy. Magnetic resonance imaging of the brain and orbits with and without contrast revealed a left cavernous sinus mass. The patient was transferred to the Smilow Cancer Hospital at Yale-New Haven and received gamma knife radiosurgery for the presumed neoplastic lesion.

**Conclusion:** Although support can be made for both a “wait-and-see” approach and acute diagnostic imaging, our case highlights the benefits of early imaging. Appropriate acute neuro imaging in patients with presenting isolated sixth nerve palsies can be lifesaving.

### Keywords

Cranial nerve palsy, acute, isolated, magnetic resonance imaging (MRI)

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### Cover Page Footnote

Acknowledgment: We thank David V. Mignardi for his original, creative illustration: Figure 1.

## BACKGROUND

Traditionally, eyecare providers employ a wait-and-see approach with respect to older patients presenting with a presumed vasculopathic isolated sixth nerve palsy. However, given review of recent literature and the potential of morbidity in these patients, acute neuroimaging should be strongly considered. Eyecare providers are often faced with challenging decisions when patients present with acute isolated oculomotor nerve palsies. This case highlights the diagnostic dilemma of an older patient with significant vasculopathic risk factors who presents with an isolated sixth nerve palsy. For patients older than 50, a vasculopathic etiology is the most likely cause, however, a small but significant percentage of these patients may suffer from a more ominous condition such as, giant cell arteritis, intracranial mass, or aneurysm. As evidenced by our case, acute neuro imaging should be considered in all isolated sixth nerve palsies.

## CASE REPORT

A 69- year old Caucasian male presented to clinic with new onset constant, horizontal, binocular diplopia at distance and near with and without correction. The patient reported the diplopia had been intermittent for a couple of months but became constant two days prior. He also stated he had intermittent orbital pain and pressure in the left eye and occasional headaches for the last two years. About the same time as the onset of constant double vision, he noted his ongoing orbital discomfort had become more constant (3 out of 10 pain scale). The patient denied symptoms related to giant cell arteritis such as jaw claudication, scalp tenderness, weight loss, fever, or malaise. He also denied dysphagia, dysarthria, paresthesia, vertigo, nausea, photosensitivity, or vision loss. The patient had no recent facial or ocular trauma.

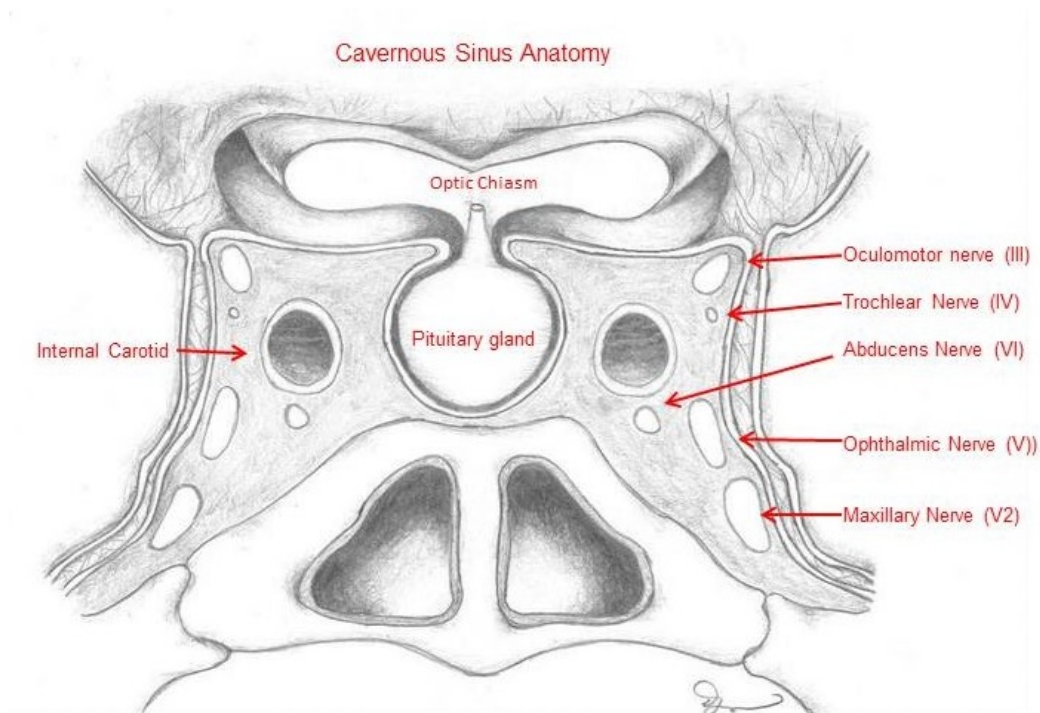
The patient's medical history included a 40 year history of insulin-dependent diabetes with periods of poor blood glucose control. His most recent hemoglobin A1c was 7.1% taken 1 year prior to the exam. Systemic history was also positive for hypertension, hyperlipidemia, hypothyroidism, and cutaneous melanoma on the right forearm excised 15 years ago without complications or recurrence. The patient was taking insulin, hydrochlorothiazide, lisinopril, metformin, and levothyroxine. Ocular history included mild non-proliferative diabetic retinopathy without macular edema, as well as a past history of retinal hemorrhages in the peripheral retina of the right eye and a Hollenhorst plaque in the left eye noted 4 years prior. A carotid doppler was ordered at that time and showed small amounts of hypoechoic (soft) and heterogeneous plaque with no hemodynamically significant

stenosis demonstrated on either side. The plaque was no longer evident on subsequent dilated eye exams.

Best corrected visual acuities were 20/25 and 20/20 with the right and left eye, respectively. Pupillary testing and confrontational visual field testing were normal in both eyes. Extraocular motility testing showed full range of motion in the right eye and restricted abduction in the left eye, but without pain on eye movement. The patient reported horizontal diplopia in all fields of gaze which worsened when the patient looked to his left. Von Graefe at distance revealed 9 prism diopters of esotropia in primary gaze. (Although ocular deviation was not measured in all fields of gaze during this exam. However, testing for comitancy provides important information for localizing the cause of the diplopia and should be performed for all presenting diplopia cases.) Close observation noted that neither eye was pulsatile nor proptotic.

Anterior segment findings were unremarkable and intraocular pressures were measured at 16 mm Hg in the right eye and 17 mm Hg in the left eye. Dilation revealed normal optic nerve cupping and no evidence of disc edema in either eye. There was mild non-proliferative diabetic retinopathy without macular edema in both eyes, stable from the previous examination one year prior. The patient was diagnosed with an isolated left sixth nerve palsy and was prescribed a 9 prism diopter Fresnel lens to alleviate his diplopia. The amount of prism prescribed was decided upon based on his 9 prism diopter esotropia. This amount was trialed in office and the patient was comfortable. Given his strong vasculopathic history, no further work-up was performed. The patient was advised to return in one month to monitor his condition and was advised he should return urgently if there were any worsening of his symptoms or change in vision.

One week later the patient returned, stating he no longer had double vision; however, his diplopia was eliminated due to a new significant left ptosis. His entering acuity did not change from the previous exam, nor did his pupillary responses or confrontation visual field results (with his left upper lid manually elevated). Motilities in the right eye were still normal. The left eye, however, now showed a mild superior, inferior, and adduction deficit, in addition to his new ptosis and previous abduction deficit. The patient also reported pain in the left eye on attempted abduction. All other cranial nerve testing were unremarkable. Again, the patient was dilated, and all posterior segment findings were unchanged from the previous examination. Given the new clinical findings, the patient was now demonstrating multiple cranial nerve abnormalities with the left eye, involving both the sixth nerve and a pupil-sparing third nerve. Due to this new cranial nerve involvement, there was a strong suspicion of a non-vascular etiology. Pathology



was suspected in the cavernous sinus due to the nature of the patient's clinical signs and symptoms. Differential diagnoses included but were not limited to: giant cell arteritis, cavernous sinus tumor, cavernous sinus aneurysm, and Tolosa-Hunt syndrome. (See figure 1 for an illustration of the normal anatomy of the cavernous sinus.)

Figure 1: Illustration of the cavernous sinus showing location of cranial nerves III, IV, VI.

An erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), complete blood count (CBC) with differentials, as well as a magnetic resonance imaging (MRI) of the brain and orbits with and without contrast were ordered. Imaging revealed a 1.1 x 0.8 centimeter, ill-defined, hypointense, mass lesion in the left cavernous sinus which abutted the pituitary gland (see Figure 2).



Figure 2: Magnetic resonance image (MRI) with contrast of patient's cavernous sinus region demonstrating 1.1 x 0.8 cm, ill-defined, hypo-intense mass on the left cavernous sinus.

The optic chiasm and other midline structures were unremarkable as well were the visualized portions of orbits and paranasal sinuses. A definitive diagnosis could not be made based solely on imaging, but the possibilities included: cavernous meningioma, cavernous internal carotid artery aneurysm, and cranial nerve schwannoma. The previous blood work results returned with a normal sedimentation rate, but an elevated C-reactive protein value. Platelets were also slightly elevated but given the lack of giant cell arteritis symptoms and the abnormal imaging findings, giant cell arteritis was no longer suspected. The patient was referred urgently to the local cancer center and underwent gamma knife radiosurgery of the cavernous sinus for the neoplastic lesion. Shortly thereafter, this patient was diagnosed with high risk diffuse large B-cell lymphoma after a biopsy was performed on a symptomatic abdominal mass and he has been treated with chemotherapeutic agents since.



The patient was seen for follow up one month after the initial exam. The patient stated his double vision returned once his ptosis improved after receiving radiotherapy treatment. His entering acuity did not change from the previous exam, nor did his pupillary responses or confrontation visual fields. Motilities in the right eye were normal and the left eye showed improvement, but there was a continued presence of a left ptosis and deficits in left superior adduction, inferior adduction, superior abduction, inferior abduction, and abduction (see figure 3).



Figure 3: (A-I) Patient at one month follow-up. Right upper gaze with left adduction deficit (A). Normal superior gaze (B). Left superior gaze with left abduction deficit (C). Normal right lateral gaze (D). Primary gaze illustrating improved left ptosis (E). Left lateral gaze deficit (F). Right inferior gaze with mild left adduction deficit (G). Normal inferior gaze (H). Inferior left gaze with left abduction deficit (I).

## DISCUSSION

Clinical decisions can be challenging with older patients who present with acute diplopia secondary to a non-traumatic, neurologically isolated unilateral abducens palsy. Commonly, a vascular etiology is suspected in an isolated unilateral

abducens palsy in patients older than 50 years of age with a long history of vasculopathic risk factors such as, diabetes, hypertension, ischemic heart disease, and peripheral vascular disease.<sup>1</sup>

There are several studies that support a “wait-and see” approach. A retrospective analysis in 2004 by Patel et al. revealed 84% of non-traumatic isolated unilateral abducens palsy were either undetermined or associated with hypertension or diabetes. Of the 32 undetermined cases, 26 underwent neuroimaging which was unremarkable, and 75% of the undetermined cases resolved spontaneously. The authors recommended careful observation of isolated sixth nerve palsies in patients that have a history of vascular pathology and, if progression ensues, then further evaluation and neuroimaging is warranted.<sup>2</sup> Similarly, a prospective analysis in 2011 by Murchison et al. found a low yield: 1 in 94 patients with acute isolated cranial nerve III, IV and VI palsies were found to have a treatable cause. Notably, the single patient in the study that did have a treatable cause was a patient with a CN VI palsy secondary to a pontine hemorrhage detected with gadolinium-enhanced magnetic resonance imaging. Based on their study, a “wait-and-see” approach was advised with acute mononeuropathies unless the patient is younger than 50, has a history of cancer, exhibits other neurologic signs or symptoms, has a pupil involving or partial cranial nerve III palsy, or fails to resolve three months after onset.<sup>3</sup> The Sankara Nethralaya Abducens Palsy Study found approximately 6% of isolated, non-traumatic, sixth nerve palsies were secondary to undiagnosed causative lesions. Notably, their recommendations for imaging advise an individualistic approach with each patient. For those patients over 50, with known vascular risk factors, they propose managing risk factors and monitoring weekly. However, any worsening in symptoms, non-improvement at 3 months, or involvement of other cranial nerves would prompt immediate neuroimaging. Additionally, those patients greater than 50 without vasculopathic risk factors would require immediate neuroimaging as would those with any history of malignancy.<sup>4</sup>

However, significant controversy exists in the literature whether immediate neuroimaging is warranted in acute, isolated, sixth nerve palsies. In another study, Bendszus et al. recommended all patients with isolated sixth nerve palsies have magnetic resonance imaging done at the initial visit regardless of the patient’s vasculopathic risk factors. Their prospective study of 43 patients (age ranging from 6-72 years of age) found 63% of patients had a causative lesion, most of which were tumor or tumor-like found on high resolution magnetic resonance imaging. The patients with pathology on MRI were younger, with a mean age of 43, and had less vascular risk. However, 15% of patients with a causative lesion on MRI also had a history of vascular disease, supporting the authors’ recommendations for early neuroimaging.<sup>5</sup> In another prospective analysis by Chou et al., 66 patients,



52-85 years of age were evaluated with magnetic resonance imaging or computerized tomography at initial presentation of an acute isolated III, IV, or VI nerve palsy. Despite the high prevalence of microvascular disease in this population, 14% of patients were found to have another cause identified on imaging. Neoplasm, brainstem infarct, demyelinating disease, and pituitary apoplexy were among the causes of isolated sixth nerve palsy.<sup>6</sup> According to their study, more than 50% of patients having a causative lesion on imaging did concurrently have one or more vascular risk factors. These authors advocated that the findings were significant enough to strongly contemplate imaging all adults with acute ocular mononeuropathies.<sup>6</sup> Similar findings were reported by Paz et al.: 7% of acute isolated fourth or sixth nerve palsies had causes other than presumed microvascular ischemia. Interestingly, the sixth cranial nerve had the highest incidence of other causes (80%) and etiologies included pituitary macroadenoma, brain metastasis from metastatic hepatocellular carcinoma, and myasthenia gravis. This study emphasized the importance of neuroimaging on patients with acute isolated 4<sup>th</sup> or 6<sup>th</sup> nerve palsies despite expense and potential low yield. The authors stressed the decision to image is individualistic and should be based on a detailed history and thorough examination.<sup>7</sup>

Similarly, a multicenter prospective study by Tamhankar et al. of 109 patients over the age of 50 found 16.5% who presented with acute isolated ocular motor cranial neuropathy had a causative etiology other than microvascular. This study's analysis highlighted giant cell arteritis and isolated mononeuropathies. Giant cell arteritis was diagnosed in three patients, all of whom presented with isolated abducens palsies, none of whom reported classic symptomatology. This study highlights the importance of giant cell arteritis testing in patients over the age of 50 with or without the classic symptoms of unilateral headache, fever, weight loss, malaise, musculoskeletal symptoms, and polymyalgia rheumatica. Testing for ESR, CRP, and platelets can prevent a missed diagnosis of giant cell arteritis and avoid irreversible severe vision loss. Giant cell arteritis testing should be performed at initial presentation in a patient with an isolated nerve palsy regardless of vascular history. Additionally, when excluding giant cell arteritis, there was approximately a 1 in 20 chance a vasculopathic patient with an isolated fourth or sixth nerve palsy will have another cause for their palsy. These authors also point out that the cost effectiveness of early MRI in their study compares favorably to other conditions that routinely utilize imaging, such as patients with headaches and non-focal neurologic examinations. The authors argue a normal MRI in a patient with acute diplopia will help alleviate fears of a brain tumor or other serious disease and may have significant social, psychologic, and economic benefits as relating to productivity.<sup>8</sup> Most recently, Elder et al. published an update of the evaluation and management of isolated sixth nerve palsy. They stressed the importance of a thorough clinical history, physical examination, and proper magnetic resonance

imaging technique (including gadolinium) to avoid missing conditions which mimic sixth nerve palsies. Based on their review of the literature, they advocate for acute neuroimaging in all cases of isolated sixth nerve palsy, even those with obvious vasculopathic risk factors.<sup>9</sup>

A history of cutaneous melanoma, such as with our patient, could potentially press the need for early imaging. The survival rate of metastatic melanoma at 5 years is poor at 5%-19%.<sup>10</sup> In our case, the patient's one time history of cutaneous melanoma was about 15 years ago without mention of metastatic conversion. If it had metastasized, this patient would likely be aware of the diagnosis, or would have passed away from the disease. Because of the remote history of melanoma with no known metastasis, we chose not to neuroimage at initial presentation. With that said, any recent diagnosis of melanoma or other cancers could prompt early imaging of isolated nerve palsies given the unknown timeline of metastatic conversion. Of interest, the likelihood of secondary melanoma in the cavernous sinus is exceedingly rare with only a handful of documented cases.<sup>11</sup>

## CONCLUSION

Previously, the guidelines of whether to obtain neuroimaging for a patient with an isolated sixth nerve palsy were on the conservative side. No imaging was recommended if a patient had an isolated mononeuropathy and a significant vasculopathic history. However, a recent study showed that patients with an isolated nerve palsy and vascular risk factors can have another underlying cause identified on imaging in around 15% of cases.<sup>5</sup> Although 15% may not seem that significant, many of these detected anomalies can be important and time sensitive such as neoplasms or demyelinating disease. Conversely, early imaging should be strongly considered in patients younger than 50, if new neurologic symptoms appear, or if the palsy does not resolve in 3 months regardless of vasculopathic history. In patients over 65, temporal arteritis should be considered, regardless of whether the patient exhibits the classic symptoms. Lastly, any patient with a history of suspected or confirmed metastatic cancer should undergo early imaging. Although continued support can be made for a "wait-and-see" approach, we believe that paradigm should not be as steadfast as once thought. If imaging is readily available, and if not cost prohibitive, there is value both diagnostically and psychologically in obtaining immediate neuroimaging in new cases of isolated cranial nerve palsies.

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