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Ischemic Cranial Nerve III Palsy: Diagnosis, Management, and Follow-up

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Ischemic Cranial Nerve III Palsy: Diagnosis, Management, and Follow-up

Abstract

Background: Acquired cranial nerve III palsies (CN3P) can be ischemic in nature due to underlying vasculopathy, trauma, or by compressive damage due to aneurysm or tumor. In most cases, neuroimaging is completed to rule out a life-threatening etiology. This case outlines an acute oculomotor palsy due to ischemic microvascular disease with the appropriate diagnostic testing, treatment, and follow-up course.

Case Report: A 67-year-old African American female presented with complaints of a drooping left eyelid and intermittent diagonal diplopia. She had a known diagnosis of type 2 diabetes and hypertension. Entering visual acuity was 20/25-1 in the right eye (OD) and 20/40-1 left eye (OS). No afferent pupillary defect was noted OD or OS, however, a sluggish response to light was noted OS. Entrance testing was unremarkable OD. CVF were restricted superiorly OS due to an incomplete ptosis and EOMs were restricted in all gazes except abduction with the eye in a down-and-out position. The patient was sent to the emergency room to rule out a pupil involving CN3P. All testing was unremarkable and a final diagnosis of an ischemic CN3P was made.

Conclusion: Prompt diagnosis and neuroimaging is essential in the management of acute CN3P. Clinicians must pay close attention to the pupils as it may reveal the etiology. In this case, the pupil response warranted immediate referral to rule out potential life-threatening etiology. Fortunately, the etiology was determined to be ischemia to the oculomotor nerve from her uncontrolled systemic vasculopathies. Such patients should be monitored regularly until resolution.

Keywords

Cranial Nerve III Palsy, Oculomotor Nerve, Diabetes, Ischemic, Rule of the Pupil, Aberrant Regeneration

INTRODUCTION

An acquired cranial nerve III palsy (CN3P) can be ischemic in nature due to underlying vasculopathy, trauma, or by compressive damage due to an aneurysm or tumor. Assessing pupil function can be useful in deciphering aneurysmal versus ischemic etiology. It is also important to recognize cases in which this cannot be applied. In most cases, neuroimaging is completed to rule out a life-threatening etiology. This case outlines an acute oculomotor palsy due to ischemic microvascular disease with the appropriate diagnostic testing, treatment, and follow-up course.

CASE REPORT

A 67-year-old African American female presented to the urgent care clinic with complaints of pain around the left eye for one week. She reported pain spreading from around the left orbit down to the left cheek. Three days prior, she had been diagnosed with an abscess of the left jaw and was started on an unknown oral antibiotic by her dentist. She noted associated blurry vision, intermittent "diagonal" diplopia, and ptosis of the left eye (OS) for roughly two days prior to initial presentation. Her last ocular examination, roughly three years prior, was remarkable for presbyopia, incipient cataracts, and type 2 diabetes without retinopathy or macular edema. The patient's medical history was positive for hypertension, hypercholesterolemia, and type 2 diabetes. She reported her last blood sugar four days prior to presentation was 416 milligrams per deciliter (mg/dL) after eating and her last hemoglobin A1c (HbA1c) five months prior as roughly 9-10%. Systemic medications included rosuvastatin, pantoprazole sodium, metformin hydrochloride, lisinopril- hydrochlorothiazide, Lantus®, and Humalog®. She denied any history of surgeries or trauma and had no known medical allergies. Family history was unremarkable. Social history was negative for tobacco, alcohol, or recreational drug use. She wasoriented to person, place, time, and her mood was appropriate.

Corrected distance visual acuities were 20/25-1 in the right eye (OD) and 20/40-1 OS. Distance pinhole acuity OS showed no improvement. Pupil measurements were determined to be 3.5 mm OD and 4 mm OS in bright illumination and 4.5 mm OD and 5 mm OS in dim illumination. Pupils were round and reactive to light OD and OS, however, with a sluggish pupil response OS. No afferent pupillary defect (APD) was noted OD or OS. Confrontation visual fields (CVFs) were full to finger

count (FTFC) OD and constricted superiorly OS due to an incomplete ptosis. With the upper eyelid lifted OS, CVFs were FTFC. Extraocular muscles (EOMs) were unrestricted in all gazes OD, while eye movements OS were restricted in all gazes except abduction with the eye in a down-and-out position. External examination revealed an almost complete ptosis of the left upper eyelid (Figure 1). Biomicroscopy revealed normal palpebral conjunctiva, bulbar conjunctiva, sclera, puncta, and cornea in both eyes (OU) with 1+ meibomian gland dysfunction (MGD) in both eyes. The anterior chambers were deep and quiet OD and OS, and the anterior chamber angles were estimated Grade 4 by Van Herick estimation. Iridies were flat and brown without neovascularization OU. Grade 1 nuclear sclerotic cataracts were present in each eye. An undilated fundus examination revealed a normal vitreous without posterior vitreous detachment OU. The optic nerves were flat, sharp, well-perfused OU without neovascularization of the disc, and the cup-to-disc ratio was 0.35 horizontal (H) /0.35 vertical (V) OU. There were scattered paramacular dot hemorrhages present OU, without clinically significant macular edema. Retinal arterioles were attenuated OU without signs of neovascularization. The peripheral retinae were not viewed at this time as an immediate referral to the emergency room was deemed necessary.

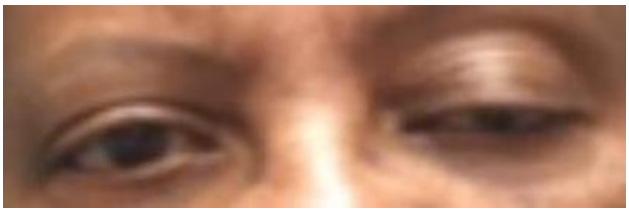

Figure 1: External photography at initial presentation showing an almost complete ptosis of theleft upper eyelid with the left globe in a down-and-out position.

The differential diagnoses for this case included:

- Cranial nerve III palsy – damage to the oculomotor nerve resulting in ocular motility restrictions, ptosis, and possible pupil involvement on theaffected side. CN3P can be congenital or acquired due several etiologies,including vascular disorders, tumors, inflammation, or trauma.[1]
- Myasthenia gravis – an autoimmune neuromuscular disorder responsible for weakness of skeletal muscles including those responsible for chewing, swallowing, facial expression, eye movements, and eyelid movements. Patients typically note progressive muscle weakness worsened toward the

end of the day or after periods of activity. Pupil involvement is not typically observed. [2]

- Giant cell arteritis – an inflammation of medium sized arteries typicallyin patients over 50 years of age. Vasculitis can lead to ischemia resultingin patient symptoms including headache, jaw claudication, neck pain, scalp tenderness, anorexia, malaise, and fever.[3]
- Congenital ptosis – benign, abnormal drooping of the upper eyelid which can be present at birth or occurs within the first year of life. Associated long-term sequelae can include deprivation amblyopia, anisometropia, and cosmetic concerns for children.[4]
- Superior orbital fissure syndrome – compression of structures just anterior to the orbital apex which is most commonly a result of trauma.Clinical findings include oculomotor, trochlear, and abducens nerve palsies, a fixed and dilated pupil, proptosis, lacrimal hyposecretion, andloss of corneal sensitivity. This condition does not result in optic nerve involvement.[5]

The patient denied a history of longstanding ptosis, nor progressive muscle weakness that worsened toward the end of the day. The patient did not report any jaw claudication, scalp tenderness, or headache, and no additional neurological involvement was noted. Therefore, myasthenia gravis, giant cell arteritis, congenital ptosis, and superior orbital fissure syndrome were considered as less likely diagnoses. The patient was diagnosed with a complete cranial nerve III palsy OS with concern for relative pupil involvement due to the sluggish response to light OS.

An immediate referral to the emergency room was made to rule out life-threatening compressive or vascular etiologies. Blood work was recommended including complete blood count with differential, erythrocyte sedimentation rate, C-reactive protein, fluorescent treponemal antibody absorption, and rapid plasma regain to rule out infectious etiology. The patient was counseled on the importance of strict blood sugar, blood pressure, and cholesterol control as her uncontrolled systemic vascular health was highly suspected to be the underlying

cause of her condition. A follow-up ocular examination was scheduled for six days. She was advised to see her primary care physician within two weeks.

PHONE CALL #1

The patient was contacted for an update 1 day later by telephone. She stated that she had been admitted into the hospital and a computerized tomography angiography (CTA) as well as a magnetic resonance angiogram (MRA) had been completed. The on-call ophthalmology resident reported that both the CTA and MRA showed no signs of space-occupying lesions, aneurysms, or occlusive vascular disorders and that all requested blood work had come back normal. He stated that the patient was being held for close observation due to the ischemic CN3P along with a concurrent oral abscess.

PHONE CALL #2

The patient called five days later (six days after initial onset) to report that she was told her CN3P was caused by her "nerves not receiving enough blood." She was expected to be released from the hospital later that day with an eye patch to be worn over her left eye. A follow-up had been scheduled by the hospital with their neurology department 2 weeks after discharge.

FOLLOW-UP #1

The patient returned for follow-up as directed after discharge from the hospital 6 days following initial onset. She noted a now complete ptosis of the left upper eyelid and "diagonal" diplopia with elevation of the upper eyelid. Her last blood sugar was 233mg/dL earlier that day and her last HbA1c was 12.5% 1-day prior. Corrected distance visual acuities were stable OU. The patient's blood pressure was 130/70 mm Hg, right arm seated. Pupils, CVFs, and EOMs (Figure 2) were stable OD and OS. Biomicroscopy revealed stable findings. Dilated retinal fundus examination revealed stable findings of the posterior poles and unremarkable peripheries. She was educated on the nature of the pupil- sparing CN3P with anticipation of recovery within the next 3-6 months.

Additionally, the patient was educated on the presence of mild non-proliferative diabetic retinopathy without macular edema OU and Stage 1 hypertensive retinopathy OU. The importance of strict blood sugar, blood pressure, and cholesterol control was emphasized. She was advised to follow-up with her primary care physician and to return for monthly examinations until complete

resolution. She was given the clinic's 24-hour urgent care phone number and advised to call immediately with any changes to vision or symptoms.

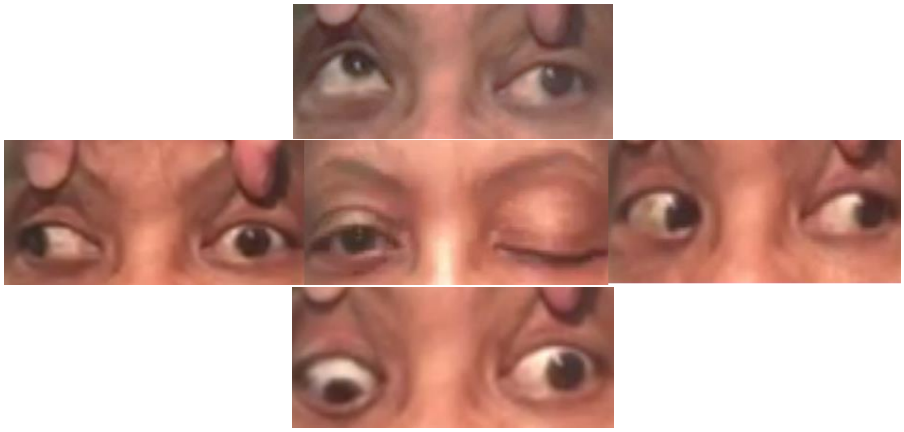

Figure 2: Extraocular motility pattern 6 days after initial onset of an ischemic, pupil sparingCN3P OS showing a complete ptosis of the left upper eyelid with restricted supraduction, infraduction, and adduction OS. Motility was unrestricted OD.

FOLLOW-UP #2

The patient returned 1 month later (2 months following initial onset) for evaluation of the pupil-sparing ischemic CN3P OS. She reported stable complete ptosis OS with diplopia when she lifted her upper eyelid. Her last blood sugar was 108mg/dL earlier that morning and her last HbA1c was 11% three weeks prior. Corrected distance visual acuities were 20/30+2 OD and 20/30 OS. Distance pinhole acuities were 20/25+2 OD, and 20/25-2 OS. Reduced best corrected visual acuity OU was attributed to grade 1 nuclear sclerotic cataracts OD and OS. Pupil, CVF, and EOM findings were stable. She was educated on the stability of her condition and directed to return in 1 month for follow-up.

FOLLOW-UP #3

The patient returned 1 month later for follow-up (3 months following initial onset). She reported stable complete ptosis OS and diplopia when the left upper eyelid was lifted. Her last blood sugar was 101mg/dL earlier that morning. Corrected distance visual acuities and all exam findings were stable. She was advised to return for follow-up in 1 month.

FOLLOW-UP #4

The patient returned 1 month later for follow-up (4 months after initial onset). She reported complete resolution of ptosis OS and denied any symptoms of diplopia,

headache, or ocular pain. Her last blood sugar was 108mg/dL earlier that morning. Corrected distance visual acuities, pupils, and CVFs were stable. EOMs were full OD and OS without restrictions. Her upper eyelid positions were equal and symmetric without ptosis OS (Figure 3). She was educated on the resolution of her condition. The importance of blood sugar, blood pressure, and cholesterol control were emphasized. She was directed to return for follow-up in 3months.

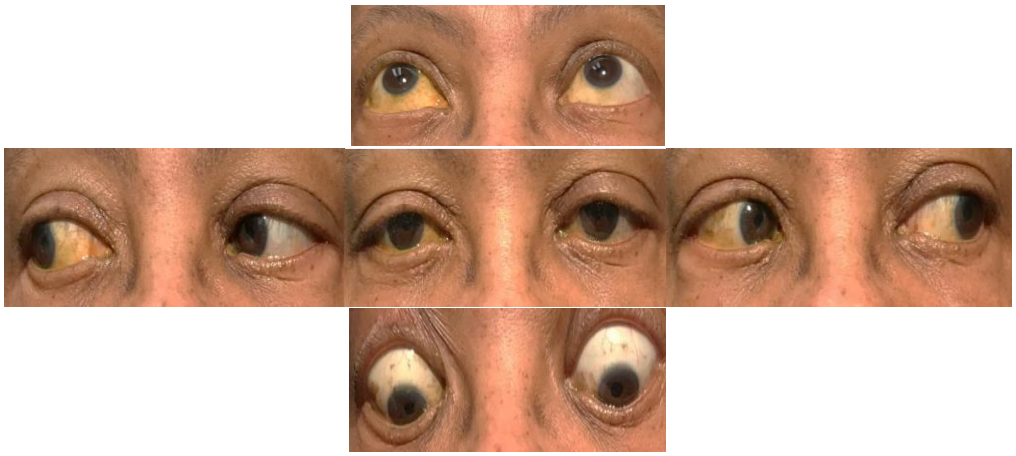

Figure 3: Extraocular motility pattern 4 months after initial onset of an ischemic, pupil-sparing CN3P OS showed unrestricted motility OD and OS as well as a complete resolution of ptosis OS.

FOLLOW-UP #5

The patient returned for follow-up 3 months later (7 months after initial onset). She reported stable symptoms and vision OU. She denied any recurrence of ptosis OS and denied any symptoms of diplopia, headache, or ocular pain. Vision and all exam findings were stable. She was educated on the stable ocular findings and informed that she could begin to be monitored yearly with comprehensive eye examinations. The importance of strict blood sugar, blood pressure, and cholesterol control along with regular follow-up examinations with her primary care physician were emphasized.

DISCUSSION

The oculomotor nerve (CN3) controls autonomic and somatic functions within the orbit. The parasympathetic autonomic function of CN3 is responsible for the innervation of the iris sphincter pupillae muscle and ciliary muscles controlling iris constriction and accommodation. The somatic function of CN3 provides innervation to the levator palpebral superioris muscle responsible for upper eyelid elevation. Innervation of the superior rectus, medial rectus, inferior rectus, and

inferior oblique muscles which are primarily responsible for elevation, adduction, infraduction and extorsion respectively are also supplied by the somatic division of CN3.[1] The large somatic motor fibers run internally within CN3 while the small autonomic parasympathetic fibers run externally.[6] The spatial orientation of the somatic and autonomic fibers within the oculomotor nerve provides insight into the cause of a third nerve palsy-based pupil involvement.

A CN3P can be congenital or acquired. Congenital CN3Ps are typically caused by malformation or raised intracranial pressure at the junction of the posterior communicating artery (PCA) and internal carotid artery (ICA). Although congenital CN3 is not life-threatening, it may indicate other congenital malformations.[1] Acquired CN3P can present as complete, incomplete, pupil-sparing, pupil-involved, isolated, or complicated by additional neurologic involvement. An incomplete, or partial, CN3P will present with a variable degree of ptosis along with variable motility patterns depending on the affected extraocular muscles. Incomplete CN3P are more common and may or may not have pupil involvement. Complete CN3P are less common and present with a full ptosis and the affected eye in the down and out position due to complete damage to the somatic function. As with a partial CN3P, pupil involvement may or may not be present in a complete CN3P.[7] Pain associated with a CN3P cannot be used to determine ischemic or compressive etiology as both present with essentially equal frequency.[8]

The majority of isolated CN3P are caused by microvascular abnormalities due to underlying vascular diseases including hypertension, diabetes, or hyperlipidema.[9] Damage to the oculomotor nerve associated with microvascular disease leads to ischemia of the internal somatic motor fibers causing ptosis and extraocular motility restrictions classically without affecting pupillary function. Compressive damage to the oculomotor nerve causes ischemia to the external autonomic fibers resulting in painful pupillary involvement in the form of a fixed, non-reactive pupil with associated ptosis and motility restrictions. While pupil involvement is a strong predictor of compression by an aneurysm at the junction of the PCA and ICA, it does not rule out microvascular cause. It has been reported that 14-32% of ischemic and 64-86% of compressive CN3P present with pupil-involvement.[9,10] Research has shown that 14% of CN3P caused by an aneurysm at the junction of the ICA and PCA present initially without pupil involvement and eventually progress to pupil involvement within 7-10 days.[8] Therefore, a lack of pupil involvement on initial presentation should not rule out aneurysmal or compressive etiology.[6,9]

There is also a “Rule of the Pupil” in association with CN3P first described by

Rucker in 1958.[11] These guidelines proposed that if a CN3P occurs without pupil involvement, it is highly suggestive of ischemic microvascular disease. On the other hand, he observed that the majority of pupil-involved CN3P were due to an aneurysm. The close proximity of the external autonomic fibers within the oculomotor nerve to the PCA and ICA results in compression of these fibers first in the case of a PCA or ICA aneurysm. Rucker's rule states that up to 97% of pupil-involved CN3P are caused by aneurysm.[10]

However, the "Rule of the Pupil" should not be applied in the following situations. First, in patients between twenty to fifty years of age in which advanced microvasculardisease is unlikely. These cases must be worked-up as an aneurysm until proven otherwise and microvascular etiology considered a diagnosis of exclusion.

Second, an incomplete CN3P has been shown more often to be caused by a slow growing aneurysm and, therefore, should be diagnosed as an aneurysm until proven otherwise. It has been documented that roughly 14% of all carotid aneurysms initially present as pupil-sparing incomplete CN3P.[10,11] The third instance in which this rule should not be followed is in the case of a CN3P with relative pupil sparing. In these patients, the affected pupil does react, however, not to the same extent as the unaffected pupil. This sluggish pupil response on the affected side is referred to as "relative" pupil-sparing. The final occasion in whichthe "Rule of the Pupil" is inappropriate to follow is a case of a complicated CN3P. If other neurologic symptoms including, but not limited to, an abduction deficit, facial weakness, proptosis, or loss of corneal sensitivity are observed in association with a CN3P regardless of pupil involvement, further work-up and imaging is necessary.[10]

In clinical practice, neuroimaging is often completed on patients presenting with an acute CN3P regardless of pupil involvement due to the potential risk of death associated with rupture of an aneurysm. Use of neuroimaging is necessary in the four abnormal clinical presentations listed above in which the "Rule of the Pupil" cannot be applied.[12] An imaging technique known as digital subtraction angiography (DSA) is considered the gold standard in the detection of an intracranial aneurysm. This modality removes all structures other than blood vessels from the image to make blood vessels more visible. However, due to the risk of stroke associated with this technique, DSA has generally been replaced with less invasive imaging techniques.[8] The most common imaging techniques currently used for CN3P include CTA and MRA.[8] In the majority of patients, both imaging

studies will be performed. In the case of a CN3P, CTA is often more sensitive in the detection of an intracranial aneurysm versus MRA. One possible hindrance of CTA is the potential for an aneurysm to be masked by nearby bony details. In this instance, an MRA would be considered superior. An additional benefit of an MRA is the lack of patient exposure to ionizing radiation as seen with a CTA.[8]

An uncommon but well documented phenomenon associated with CN3P due to aneurysm, trauma, or tumors is aberrant regeneration of the oculomotor nerve. This condition is also known as oculomotor synkinesis and occurs in roughly 15% of acquired CN3P.[13] In most instances, the oculomotor nerve will spontaneously regenerate without any complications. However, in some cases the nerve does not fully regenerate, and its axons become misdirected allowing for inappropriate innervation of different muscles.[14] There is no clear way to determine which patients will go on to develop aberrant regeneration. However, cases of CN3P due to microvascular disease never result in synkinesis.[15] There are three typical patterns of oculomotor synkinesis. The first, referred to as Pseudo Von-Graefe's Sign, presents as upper eyelid elevation with down-gaze. This phenomenon is caused by axonal misdirection from the inferior rectus to the ipsilateral levator palpebral superioris muscle.[16] Another form of oculomotor synkinesis occurs due to misdirection of axons from the medial rectus to the levator palpebral superioris muscle resulting in upper eyelid retraction with adduction. Pupil constriction upon adduction has also been documented due to aberrant connections between the axons of the medial rectus and iris sphincter muscle.[14]

After a systemic evaluation has been completed and aneurysmal or compressive etiologies have been excluded, regular follow-up is necessary. It is recommended that patients be followed every month for at least 6 months until resolution has been reached. If complete resolution is not seen by 6 months, further improvement can be expected up to one-year post onset.[17] With a complete ptosis, diplopia is typically not a concern. However, as the ptosis begins to improve, diplopia may be noted, and occlusion therapy may be necessary. If photophobia secondary to a dilated pupil is a concern, pilocarpine drops may be used for management.[17]

Conclusion

This case demonstrates the typical presentation, work-up, and management of a CN3P due to underlying vascular disease. In all patients presenting with an acute CN3P, it is important to pay close attention to the pupils. Using the "Rule of the Pupil" can play an important role in deciphering aneurysmal versus ischemic etiology. It is also important to recognize cases in which this cannot be applied. In

this case, the slight anisocoria with the sluggish pupil response warranted immediate referral for imaging to rule out potential aneurysmal or compressive etiology. Neuroimaging with MRI or CTA is done on many patients with acute CN3P to rule out the potential risk of stroke or death by rupture of an intracranial aneurysm. Fortunately, no such cause was found and this patient's CN3P was determined to be caused by ischemia to the oculomotor nerve from her history of uncontrolled hypertension and type 2 diabetes. As demonstrated in this case, aberrant regeneration of the oculomotor nerve is not seen in cases of ischemic CN3P. However, in CN3P caused by tumor, aneurysm, or trauma, incomplete recovery may occur, and misdirection of the axons may be seen causing abnormal motility or pupil patterns. As seen in this case, it is important to monitor these patients regularly for up to 6 months until resolution is observed. If complete resolution is not seen at 6 months, further improvement may be appreciated up to 1 year.

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