

Differential diagnosis and management of acquired sixth cranial nerve palsy

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KEYWORDS

Sixth nerve palsy;
Abducens nerve palsy;
Lateral rectus palsy;
Hypertension

Abstract

BACKGROUND: Cranial nerve VI innervates the lateral rectus muscle. A lesion will result in esotropia greater at distance and an ipsilateral abduction deficiency. After the age of 50 years, vascular diseases are the most commonly known causes.

CASE REPORT: A 55-year-old white man reporting a 2-week history of horizontal diplopia that was worse at distance was found to have a left sixth cranial nerve paresis. The patient was diagnosed with hypertension and placed on medications. At the 4-week follow-up visit, the abduction deficiency had resolved.

DISCUSSION: The incidence of sixth nerve palsy is 11.3 in 100,000. A lesion anywhere along the course of the nerve, from the pons to the orbit, can cause a paresis or palsy. After ruling out trauma and non-neurological problems, cases should be classified into neurologically isolated or non-neurologically isolated cases. Neurologically isolated sixth nerve palsies are associated most commonly with vascular disease. Non-neurologically isolated sixth nerve palsies typically are associated with more grave conditions.

CONCLUSION: A sixth nerve palsy of vascular or undetermined causes typically resolves within 6 to 8 weeks. If resolution does not occur within 2 to 3 months, the condition progresses, or if additional neurologic signs or symptoms develop, imaging studies are indicated.

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The sole responsibility of cranial nerve six (CN VI), the abducens nerve, is to innervate the lateral rectus muscle, which is responsible for abducting the eye. An abduction deficit, which may be complete (palsy) or incomplete (paresis), results in esotropia and ipsilateral abduction deficiency. Patients will report diplopia that is worse at distance and when looking toward the affected muscle.

A lesion anywhere along the CN VI course, from the pons to the orbit, can cause a paresis or palsy. Prompt and correct diagnosis by an eye care practitioner is critical in determining the cause and, therefore, the proper evaluation,

follow-up, and treatment. In patients older than 50 years, vascular disease or unknown causes are most common.¹ The following case presents a patient with a CN VI paresis with associated hypertension.

Case report

A 55-year-old white man presented complaining of double vision for the previous 2 weeks. The patient reported the double vision had begun gradually and had not gotten worse in the last week and a half. The diplopia was mostly at distance but was occasionally noted at near. Separation of objects was only horizontal. The patient was able to close one eye to relieve the diplopia, but nothing else seemed to

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Figure 1 Appearance of a left lateral rectus palsy in another patient. A, Primary gaze. B, Left gaze. (Courtesy of Richard London, O.D.)

help. He denied tingling or numbness in the limbs, headaches, nausea, scalp tenderness, fever, malaise, or other neurologic signs or symptoms.

The patient reported that he currently was taking amoxicillin for bronchitis. The drug had been given to him by his daughter, a nurse. No other significant medical history was reported, but the patient did not recall the last time he had seen a medical doctor. Family history included a daughter who was being treated for diabetes. The patient's most recent eye examination was 2 years prior at which time his ocular history was remarkable only for hyperopia and presbyopia.

Distance habitual visual acuities were 20/20 in the right eye (O.D.) and 20/20 in the left eye (O.S.). Cover test revealed 14 Δ left esotropia at distance and 4 Δ esophoria at near through the habitual prescription (+1.50 diopter of sphere in both eyes (OU) with +2.00 add). Two years previously, the phoric posture was orthophoric at distance and 14 Δ exophoric at near through the same prescription. Extraocular muscle movements were unremarkable O.D. However, in left gaze the left eye was unable to fully abduct. The patient could abduct the left eye occasionally to approximately 20 degrees, but in general the eye would not move past the midline. (Figure 1 shows a different patient with a left lateral rectus palsy, with the eyes in primary gaze [see Figure 1, A] and in left gaze [see Figure 1, B].) Pupils were equal, round, and reactive to light with no afferent pupillary defect noted OU. Confrontation fields were full to finger counting O.D. and O.S.

Intraocular pressures were 16 mmHg O.D. and O.S. with Goldmann applanation tonometry. Anterior segment evaluation was unremarkable OU. Results of a dilated examination of the posterior pole were unremarkable with the exception of a slightly reduced artery to vein size at a ratio of 1:2 OU. Automated visual field perimetry findings (30-2) were unremarkable OU. With the patient sitting, blood pressure in the right arm at 4:40 PM was 166/114 mmHg.

The patient had a left abduction deficit diagnosed. Because of his age, the etiologies that were considered included vascular disease, cerebral vascular accident, aneurysm, tumor, trauma, giant cell arteritis (GCA), and myasthenia gravis. Because of the in-office blood pressure reading, lack of trauma, the constant nature of the palsy, and the absence of other neurologic signs or symptoms, the etiology was suspected to be hypertension.

The patient was educated regarding the possible causes of the diplopia and was referred to a primary care physician

for follow-up care of his hypertension. The patient was given the option of eliminating the double vision by patching one eye or using Fresnel prisms, but he declined, saying that he preferred to just close an eye to eliminate the double vision. The patient was instructed to return in 4 weeks for follow-up of the double vision.

The patient was seen by a primary care physician who diagnosed hypertension, for which one 20-mg tablet of lisinopril per day was prescribed.

At the 4-week follow-up visit, the patient reported that the double vision had resolved completely 1 week after beginning the lisinopril. Distance habitual visual acuities were 20/20 O.D. and O.S. Cover test results found 2 Δ exophoria at distance and 4 Δ exophoria at near through his habitual prescription. Extraocular muscle movements were full O.D. and O.S. Blood pressure measurement in the right arm at 3:00 PM with the patient sitting was 126/92 mmHg.

The patient was educated on the importance of controlling the blood pressure and the importance of continued visual and general health care.

Discussion

Epidemiology

The incidence of CN VI palsy is 11.3 in 100,000.¹ An abducens nerve palsy is the most common extraocular muscle palsy.^{2,3} The incidence of CN VI palsy and coexisting medical conditions throughout life are shown in Table 1. Population-based studies found a higher percentage of cases associated with vascular diseases than studies done with tertiary, referral-based data. A higher rate of neoplasm was found in tertiary, referral-based studies.

Causes of acquired CN VI palsies differ depending on the age of the patient. The peak incidence of CN VI palsy is between age 60 and 70 years.¹ Within this age range, the most common associations were found to be undetermined (31%), hypertension (20%), and concurrent hypertension and diabetes (17%).¹ CN VI palsies in children most commonly are postviral in nature or caused by tumor or trauma.^{3,4} Common causes in young adults are central nervous system mass, demyelinating disease, or idiopathic causes.⁵ Vascular disease or unknown causes are most common in

Table 1 Incidence of sixth nerve palsy with coexisting medical conditions¹⁻³

Condition	Incidence (%)
Undetermined	26% to 30%
Vascular	13% to 35%
Trauma	12% to 17%
Multiple sclerosis	4% to 7%
Neoplasm	5% to 21%
Aneurysm	2% to 4%

Table 2 Causes of localizable sixth nerve palsies^{7,8}

CN VI Pathway	Pathology
Pons	Infarction
	Demyelination
Subarachnoid space	Tumor
	Neoplasms
	Head trauma
	Meningitis
	Hydrocephalus
	Pseudotumor cerebri
	Decreased intracranial pressure from a lumbar puncture
Cavernous sinus	Middle ear infections
	Inflammation
	Tumors
Superior orbital fissure	Aneurysm
	Inflammatory pseudotumor
	Metastatic tumor
	Trauma

adults older than 50 years.¹ Less common associations in adults older than 50 years are trauma, tumors, cerebral vascular accident, aneurysm, and increased intracranial pressure.¹

Anatomy and etiology

Localization of a lesion is essential in determining a cause of a lateral rectus palsy and for properly ordering neuroimaging. The function of the abducens nerve is solely to innervate the lateral rectus muscle and abduct the eye. However, because of its close proximity to other nerves throughout its cranial course, lesions are likely to produce additional neurologic signs and symptoms rather than a neurologically isolated lateral rectus palsy. Knowledge of the path of the abducens nerve from the pons to the lateral rectus muscle will facilitate the use of associated signs and symptoms to localize a lesion. Possible causes of CN VI palsy through its course are shown in Table 2. (For brevity, the term *palsy* will be used for both *palsy* and *paralysis*.)

The abducens nucleus is located in the lower part of the pons beneath the floor of the fourth ventricle (see Figure 2). Because the CN VI nucleus has projections to the medial longitudinal fasciculus (MLF), a lesion at the level of the CN VI nucleus will not produce an isolated CN VI palsy.^{6,7} The MLF projects to the contralateral oculomotor nucleus to coordinate lateral gaze with the medial rectus in the opposite eye. Therefore, a lesion involving the CN VI nucleus will cause an ipsilateral gaze palsy with sparing of vergence movements rather than an isolated abduction deficit.⁶ A lesion near the nucleus can also cause an ipsilateral facial palsy. The facial nerve (CN VII) courses around the CN VI nucleus and is in close proximity to the abducens fascicle (see Figure 2). This close relationship accounts for the frequent concurrent damage.

Axons of CN VI emerge from the brainstem in the groove between the pons and the medulla oblongata (see Figure 3). The nerve continues forward in the subarachnoid space taking a sharp bend over the petrous portion of the temporal bone before piercing the dura and entering the cavernous sinus. Lesions between the brainstem and cavernous sinus may produce either unilateral or bilateral lateral rectus palsy. Depending on the cause, many other neurologic symptoms may be present including papilloedema, facial pain or numbness, or facial nerve palsy.

The abducens nerve shares the cavernous sinus with the oculomotor nerve (CN III), the trochlear nerve (CN IV), the ophthalmic and maxillary divisions of the trigeminal nerve (CN V), and the internal carotid sympathetic plexus. A lesion in the cavernous sinus can cause other extraocular muscle problems as well as facial pain or numbness. Because of the close proximity of the abducens nerve to the internal carotid, CN VI is often involved early in cases of an intracavernous carotid aneurysm.⁸ For a short period in the cavernous sinus, the sympathetic fibers are in close proximity to the abducens nerve. A lesion in this area will cause a simultaneous CN VI palsy and Horner's syndrome.⁷

CN VI leaves the cavernous sinus to enter the orbit through the superior orbital fissure and then to innervate the lateral rectus muscle. Damage in the area of the superior orbital fissure would likely affect other cranial nerves including CN III, CN IV, and the ophthalmic division of CN V. A lesion in this area can also cause proptosis.⁷

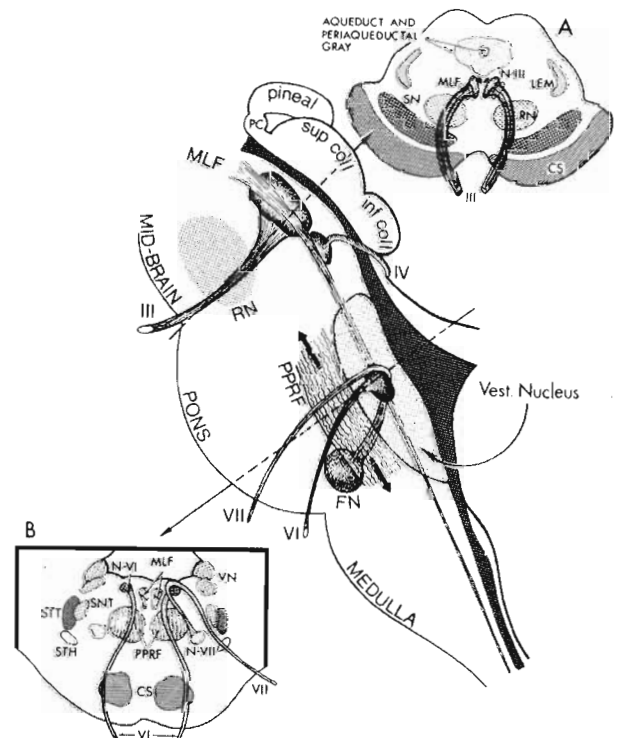


Figure 2 The relationship of CN VI nucleus to the MLF and CN VII. (Reprinted with permission from Glaser JS, Siatkowski RM. Infranuclear disorders of eye movement. In: Glaser JS, ed. Neuro-ophthalmology, 3rd ed. Philadelphia: Lippincott Williams & Wilkins;1999. Copyright © 1999 Lippincott Williams & Wilkins.)

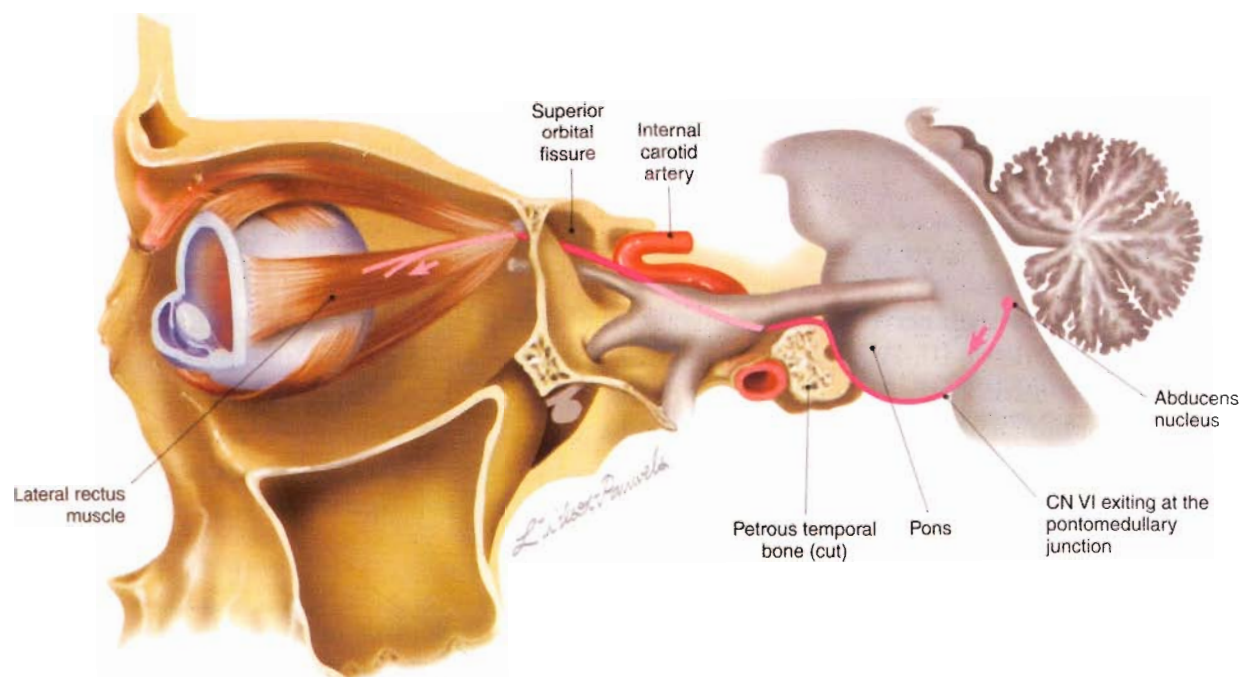


Figure 3 The route of CN VI from the pons to the lateral rectus muscle. (Reprinted with permission from Wilson-Pauwels L, Akesson EJ, Stewart PA, et al. *Cranial Nerves in Health and Disease*, 2nd ed. Copyright © 2002 BC Decker.)

Differentiation between a neurologically isolated CN VI palsy and a non-neurologically isolated CN VI palsy is critical. A neurologically isolated CN VI palsy is predominantly associated with vascular or undetermined causes. However, 50% of nontraumatic cases that involve other neurologic signs or symptoms such as papilledema, ataxia, nystagmus, nausea, vomiting, headaches, hemiparesis, and facial nerve palsies are associated with more serious medical conditions such as cerebrovascular accident, neoplasm, or aneurysm.¹

The most common causes of neurologically isolated CN VI palsies are not as grave. Eighty-three percent of nontraumatic, neurologically isolated palsies are associated with either undetermined etiology (34%), hypertension (28%), coexistent hypertension and diabetes (17%), or diabetes alone (4%).¹ Eight percent are associated with multiple sclerosis and only 2% are associated with neoplasm.¹ Patel et al.¹ found that most cases associated with multiple sclerosis (63%) and all cases of neoplasm that presented as a neurologically isolated CN VI palsy had been diagnosed before the onset of the palsy. The study found no new cases of neoplasm or aneurysm when the CN VI palsy was neurologically isolated.

Not all abduction deficits indicate a CN VI problem. Differential diagnoses should include thyroid-related restrictive myopathy, myasthenia gravis, orbital pseudotumor, and congenital defects such as Duane's retraction syndrome.

In thyroid-related restrictive myopathy, the extraocular muscles are enlarged. These patients often will have other ocular signs and symptoms such as dry eye, lid retraction, lid edema, and proptosis. Most commonly the inferior rectus

becomes fibrotic restricting upward gaze. However, fibrotic contraction of the medial rectus can produce an abduction deficit that mimics a CN VI palsy. Forced duction testing is positive in these patients indicating an increased resistance to induced rotation of the eye. B-scan ultrasonography as well as computer tomography or magnetic resonance imaging (MRI) scanning may be helpful in identifying increased muscle size.

Isolated CN VI palsy is an unusual presentation in myasthenia gravis patients. Additional testing for myasthenia gravis typically is not required unless the history is suggestive of the condition.¹ Increased diplopia with fatigue, variability of the condition, or ptosis may indicate the need for intravenous edrophonium testing to rule out myasthenia gravis.

Orbital pseudotumor, or idiopathic orbital inflammation, is a diagnosis of exclusion. It results in a tumorlike mass in the orbit that restricts extraocular muscle movement and usually involves proptosis as well as pain, swelling, and erythema.⁹ This condition typically has a rapid onset and responds to systemic corticosteroids, although there is a fibrosing type that is not responsive to steroids.

A CN VI palsy often is confused with Duane's retraction syndrome. Duane's retraction syndrome is a type of congenital lateral rectus palsy. The most common form of Duane's retraction syndrome involves a limitation of abduction and a narrowing of the palpebral fissure with globe retraction on adduction.⁴ In general, these patients are asymptomatic, but their complaints can include intermittent diplopia, fatigue, and eyestrain with near tasks.⁴

Evaluation

A CN VI palsy typically presents as a horizontal, binocular diplopia. Esotropia is usually present in primary gaze and is worse at distance and in lateral gaze in the direction of the paretic muscle. The patient also may have an abnormal head posture with the face turned toward the palsied eye. The abduction deficit may be complete (palsy) or incomplete (paresis). Maximum dysfunction typically occurs at onset but may progress over several days.¹⁰ An infarct to the abducens nerve usually is sudden and painless, but occasionally the patient will report pain around the eyes.

Forced ductions are helpful to rule out mechanical limitations of eye movements such as muscle fibrosis, muscle entrapment, tumor, muscle trauma, or inflammation. Resistance, or a positive result with forced duction testing, indicates that the damage does not have a neurogenic origin.

A dilated fundus examination including evaluation of the optic nerve head is required for all patients who present with a CN VI palsy. Increased intracranial pressure can produce papilledema. Retinal vascular changes associated with hypertension and diabetes include a change in blood vessel size, retinal hemorrhages, cotton-wool spots, and hard exudates.

Additional indicated testing depends on the patient's age as well as the presence of associated neurologic findings. The cause of CN VI palsy in patients older than 50 years is most often vascular in nature. Therefore, a complete patient history regarding hypertension and diabetes is necessary. Blood pressure measurements as well as a fasting glucose level or glycosylated hemoglobin should be obtained. If signs of GCA such as headache, scalp tenderness, jaw claudication, fever, weight loss, or malaise are present, especially in patients older than 55 years, an erythrocyte sedimentation rate and C-reactive protein level should be obtained and a temporal artery biopsy should be done. Studies indicate that this testing is not necessary if the ocular motor defect is well defined and the patient is otherwise asymptomatic.¹¹⁻¹³

A careful history and examination will help differentiate patients that can be observed and those who need neuroimaging. An MRI is recommended for older adults if the CN VI palsy does not resolve within 3 to 6 months, the esotropia is progressing after 2 weeks from its onset, other neurologic signs or symptoms are present, or if the patient has a previous history of malignancy.^{1,3,14,15} Patients younger than 45 years with a CN VI palsy require a neurologic workup even if the palsy is neurologically isolated.^{5,15,16} Cerebrospinal fluid analysis may also be necessary in younger patients if neuroimaging results are inconclusive.^{5,15,17} A bilateral CN VI palsy should never be considered vascular in origin.² MRI and cerebrospinal fluid analysis are required for these patients.

Not all investigators agree with the approach to postpone neuroimaging. Following a prospective study of 43 patients with isolated CN VI palsy referred to a tertiary care center,

Bendszus et al.¹⁸ recommended that an MRI be performed on all patients with acute CN VI palsy. In this study, a lesion causing the CN VI palsy was identified in 63% of patients. However, only 15% of these patients were known to have vascular disease, and the average age of these patients was 43 years. Following established recommendations,^{5,15,16} imaging would have been performed on patients in this age group especially in the absence of vascular disease.

Treatment/prognosis

Treatment of an abducens palsy involves treating the underlying medical condition causing the palsy. Treatment of symptoms associated with CN VI palsy includes patching, prism, injection of botulinum toxin (Botox) into the medial rectus, or extraocular muscle surgery if the esotropia is longstanding. Surgery should be considered when the deviation has been stable for at least 6 months.⁷ More than 1 surgical treatment or the use of prism after surgery is often necessary.¹⁹

Approximately half of all CN VI palsies recover spontaneously approximately 3 months after onset.^{2,3,5,10} Patients with vasculopathic CN VI palsy have a better chance of recovery (69% to 86%) and recover more rapidly (4 to 6 weeks) than patients with CN VI palsy from other causes.^{2,3,10} CN VI palsy recurred in 31% to 35% of vasculopathic patients.¹⁰ If the patient had binocular vision before the lesion, it typically returns to normal after recovery. However, suppression may occur if the palsy occurs before the visual system has reached maturity (age 7 to 8 years). When recovery does not occur in adults, persistent diplopia can result.

Conclusions

Obtaining a thorough history and performing a comprehensive examination is critical to the proper treatment of patients with CN VI palsy. After ruling out trauma and non-neurological problems, each case should be classified into 1 of 2 groups: an isolated CN VI palsy or a CN VI palsy associated with other neurologic symptoms.

Patients with non-neurologically isolated CN VI palsies should undergo additional medical and neurologic testing including neuroimaging. A previous diagnosis of neoplasm would indicate further neurologic testing even if the palsy is isolated. An isolated CN VI palsy in an older patient with vasculopathic risk factors may be observed unless the condition fails to resolve within 2 to 3 months, progresses, or additional neurologic signs or symptoms develop.

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