Isolated Palsies of Cranial Nerves III, IV, and VI

Paul W. Brazis, M.D.1

ABSTRACT

In this article, isolated palsies of cranial nerves III, IV, and VI are addressed. After discussion of the pertinent clinical anatomy of cranial nerves III, IV, and VI, the isolated involvement of each of these oculomotor nerves is defined. Based on a review of the literature, methods of evaluation and follow-up of patients presenting with diplopia from lesions of these cranial nerves are presented.

KEYWORDS: Oculomotor nerve, trochlear nerve, abducens nerve, diplopia, cranial nerve palsy

Three brainstem nuclei contain the lower motor neurons that control the eye muscles: (1) the cranial nerve III (oculomotor) nucleus in the midbrain; (2) the cranial nerve IV (trochlear) nucleus at the level of the midbrain-pontine junction; and (3) the cranial nerve VI (abducens) nucleus in the lower pons. All are paired structures located in the dorsal part of the tegmentum at their respective levels. The sixth nerve innervates the lateral rectus, and the fourth nerve supplies the contralateral superior oblique. All the other ocular muscles are innervated by the third cranial nerve. Muscles innervated by neurons on the same side (ipsilateral innervation) include the lateral (sixth nerve) and medial (third nerve) recti, the inferior rectus (third nerve), and the inferior oblique (third nerve). The superior rectus (third nerve) and the superior oblique (fourth nerve) are innervated by neurons located on the contralateral side. However, the fibers to the superior rectus cross at the level of the nucleus, so that nuclear lesions result in bilateral weakness. Similarly, oculomotor nuclear lesions cause bilateral ptosis because the nuclear group for the levator of the lid is located in the midline (a single caudal subnucleus).

In this article, I will discuss isolated palsies of cranial nerves III, IV, and VI.

ANATOMY OF CRANIAL NERVES III (THE OCULOMOTOR NERVE)

The third nerve nuclear complex extends rostrocaudally for ~5 mm near the midline in the midbrain at the level of the superior colliculus. It lies ventral to the Sylvian aqueduct, separated from it by the periaqueductal gray matter, and dorsal to the two medial longitudinal fasciculi. One unpaired and four paired rostrocaudal columns can be distinguished in the oculomotor nuclear complex. The unpaired column, shared by the right and left nuclei, is in the most dorsal location and contains the visceral nuclei (Edinger–Westphal nucleus) rostrally and the subnucleus for the levator palpebrae superioris caudally. The Edinger–Westphal nucleus mediates pupillary constriction. Of the four paired subnuclei, the most medial innervates the superior rectus muscle. This is the only portion of the oculomotor nucleus that sends its axons to the opposite eye. Decussating fibers actually traverse the contralateral subnucleus for the superior rectus muscle.
rectus. Hence, a destructive lesion in one superior rectus subnucleus results in bilateral denervation of the superior recti. Laterally in each oculomotor complex there are three subnuclei: dorsal (inferior rectus), intermediate (inferior oblique), and ventral (medial rectus). Actually, neurons supplying the medial rectus are distributed into three separate areas of the oculomotor nucleus.

In the substance of the midbrain (fascicular portion), the axons of the oculomotor neurons cross the medial longitudinal fasciculus and the decussating fibers of the superior cerebellar peduncle and then diverge widely as they traverse the red nucleus before exiting on the anterior aspect of the midbrain just medial to the cerebral peduncles. Fibers for the elevators of the eye and eyelid are probably located laterally in the fascicular portion of the oculomotor nerve. In the subarachnoid space, each third nerve passes between the superior cerebellar and the posterior cerebral arteries, courses forward near the medial aspect of the uncus of the temporal lobe, pierces the dura just lateral to the posterior clinoid process, and enters the lateral wall of the cavernous sinus. Here, the nerve runs over the trochlear nerve, lying superior to the abducens nerve and medial to the ophthalmic branch of the trigeminal nerve. Once it reaches the superior orbital fissure, the oculomotor nerve divides into a superior division, which supplies the superior rectus and the levator palpebrae superioris, and an inferior division, which supplies the medial and inferior recti, the inferior oblique, and the presynaptic parasympathetic outflow to ciliary ganglion (sphincter pupillae muscle and ciliary muscles). This division into superior and inferior rami may take place also within the anterior cavernous sinus or posterior orbit, and indeed more proximally, even at a fascicular level.

### THIRD NERVE PALSY

Third nerve palsies are divided into nonisolated and isolated third nerve palsies. The isolated third nerve palsies are defined as third nerve palsies without associated neurologic findings (e.g., headache, other cranial neuropathies). Patients with evidence for myasthenia gravis (e.g., variability, fatigue, Cogan’s lid twitch sign, enhancement of ptosis) are not included in the isolated third nerve palsy group. The six types of third nerve palsies are described in Table 1.

#### Type 2: Traumatic Third Nerve Palsy

Traumatic isolated third nerve palsy (type 2) should undergo computed tomography (CT) scanning to evaluate for associated central nervous system damage (e.g., subdural or intracerebral hematoma) as indicated by associated neurologic signs and symptoms. Third nerve palsy after mild head trauma have been observed in association with otherwise asymptomatic lesions (e.g., cerebral aneurysm). Although uncommon, neuroimaging may be warranted in patients with third nerve palsy after minimal or trivial trauma to exclude mass lesions or cerebral aneurysms.

#### Type 3: Congenital Third Nerve Palsy

Congenital isolated third nerve palsy (type 3) is rare, usually unilateral, and may occur in isolation or in...
association with other neurologic and systemic abnormalities, including congenital facial nerve palsies or other cranial neuropathies, facial capillary hemangioma, cerebellar hypoplasia, gaze palsy, ipsilateral nevus sebaceous of Jadassohn, mental retardation, digital anomalies, and septo-optic dysplasia (optic hypoplasia, midbrain malformations, and hypothalamohypophyseal dysfunction).^{4,5} All patients have some degree of ptosis and ophthalmoplegia, and nearly all have pupillary involvement. In most cases, the pupil is miotic rather than dilated, probably because of aberrant third nerve regeneration, and usually trace reactive or nonreactive to light. Rarely the pupil may be spared. Amblyopia is common. Most cases are spontaneous, but familial cases have been described. Magnetic resonance imaging (MRI) is recommended in all patients with congenital third nerve palsies, mainly to investigate for associated structural abnormalities of the brain.

**Type 4: Acquired and Nontraumatic Isolated Third Nerve Palsy**

Acquired, nontraumatic isolated third nerve palsy (type 4) may occur with lesions localized anywhere along the course of the third nerve from the fascicle to the orbit.^{6}

**Isolated Third Nerve Palsy with Midbrain Fascicular Lesions**

Rarely, a unilateral or bilateral fascicular third nerve lesion may occur in isolation without other oculomotor neuropathy or neurologic signs or symptoms.^{7–11} Fascicular lesions, even when bilateral, may occasionally spare the pupil(s). Bilateral preganglionic internal ophthalmoplegia has been described with bilateral partial oculomotor fascicular lesions.^{12} Because of the intraxial topographic arrangement of fibers, fascicular lesions may cause third nerve palsy limited to specific oculomotor-innervated muscles.^{13}

Fascicular lesions have resulted in the following: (1) isolated inferior oblique muscle paresis^{14}; (2) isolated inferior rectus muscle paresis^{15}; (3) unilateral fixed, dilated pupil unassociated with other neurologic dysfunction^{16}; (4) paresis of the superior rectus and inferior oblique muscles without other evidence of oculomotor nerve involvement^{17,18}; (5) paresis of the superior and medial rectus muscles^{19}; (6) paresis of the levator muscle, superior rectus and medial rectus muscles^{20}; (7) paresis of the inferior oblique, superior rectus, medial rectus, and levator muscles with sparing of the inferior rectus muscle and pupil^{21}; (8) paresis of the inferior oblique, superior rectus, medial rectus, levator, and inferior rectus muscles with pupillary sparing^{22}; and (9) paresis of the left inferior rectus muscle, left pupil, right superior rectus muscle, convergence, and left medial rectus muscle.^{23}

Based on these clinical studies, it has been proposed that individual third nerve fascicles in the ventral mesencephalon are arranged topographically from lateral to medial as follows: inferior oblique, superior rectus, medial rectus and levator palpebrae, inferior rectus, and pupillary fibers.^{14} A rostral-caudal topographic arrangement has also been suggested with pupillary fibers most superior, followed by fibers to the inferior rectus, inferior oblique, medial rectus, superior rectus, and levator, in that order.^{21} This model also accounts for the description of “superior and inferior division” oculomotor palsies. The superior division palsy involves the superior rectus and levator muscles without involvement of other groups.^{24,25} The inferior division oculomotor palsies cause paresis of inferior rectus, inferior oblique, medial rectus, and pupillary fibers with sparing of the superior rectus and levator.^{25,26} Both divisional palsies may be associated with intraxial midbrain lesions. Thus, although superior and inferior divisional third nerve palsies have classically been localized to anterior cavernous sinus or posterior orbital lesions, a divisional third nerve palsy may occur from damage at any location along the course of the oculomotor nerve, from the fascicle to the orbit.^{25}

**Isolated Third Nerve Palsy Due to a Subarachnoid Lesion**

An isolated peripheral third nerve palsy is most often related to an ischemic neuropathy or a lesion affecting its subarachnoid portion. Third nerve schwannomas may cause a painful relapsing-remitting third nerve palsy mimicking the clinical syndrome of ophthalmoplegic migraine.^{25} Monocular elevator paresis from isolated superior rectus and/or inferior oblique dysfunction may occur in neurofibromatosis type 2 related schwannoma.^{28} The third nerve is also susceptible to trauma in the subarachnoid space, especially during neurosurgical procedures.^{29} Closed head trauma may cause third nerve palsy due to shearing injury resulting in distal fascicular damage or partial root avulsion.^{30} Walter et al^{11} described two patients with third nerve palsies precipitated by minor head trauma with negative brain CT scans; both were subsequently discovered to have ipsilateral posterior communicating artery aneurysms. Park-Matsumoto and Tazawa described a similar case.^{3}

Compression of the third nerve by an aneurysm characteristically causes dilatation and unresponsiveness of the pupil. Compressive subarachnoid lesions may occasionally spare the pupil, however. Two explanations have been proposed: (1) compression may be evenly distributed and the relatively pressure-resistant, smaller-caliber pupillomotor fibers escape injury; and (2) the lesion compresses only the inferior portion of the nerve and spares the dorsally situated pupillomotor fibers. Third nerve palsy due to an aneurysm may be incomplete with at least one element of nerve dysfunction (i.e., ptosis, mydriasis, or extraocular muscle weakness) being absent.
Prosis has been described in isolation as the sole manifestation of third nerve compression by a posterior communicating artery aneurysm. Rarely, aneurysmal third nerve palsies may even be transient and clear spontaneously. Foroozan et al described a patient with a third nerve palsy that developed in the third trimester of pregnancy and was due to a posterior communicating artery aneurysm. Prepartum complications forced postponement of surgery. The palsy spontaneously resolved over 3 weeks after delivery by C-section. Repeated angiogram showed that the aneurysmal sac had shrunk from 10 mm to 4.5 mm.

Bhatti et al described two patients with superior division third nerve palsies due to lesions involving the cisternal portion of the nerve. In one case, the superior division palsy was caused by a posterior communicating artery aneurysm, whereas in the other case, the superior branch palsy followed anterior temporal lobectomy for epilepsy.

A normal pupil in the setting of a complete somatic oculomotor paresis, however, essentially excludes a diagnosis of aneurysm (see below). A single patient has been described in whom a painless, pupil-sparing but otherwise complete oculomotor paresis was the only sign of an aneurysm arising from the basilar artery. Conversely, an isolated pupillary paralysis without ptosis or ophthalmoparesis is rarely caused by an aneurysm or other subarachnoid lesion. Koennecke and Seyfert reported a patient with a common carotid artery dissection from intraoperative trauma whose mydriasis preceded complete third nerve palsy by 12 hours.

### Isolated Third Nerve Palsy Due to a Cavernous Sinus Lesion

Lesions of the third nerve in the cavernous sinus often also involve the other oculomotor nerves, the ophthalmic branch of the trigeminal nerve, and sympathetic fibers. Sensory fibers from the ophthalmic division of the fifth cranial nerve join the oculomotor nerve within the lateral wall of the cavernous sinus. The frontoorbital pain experienced by patients with enlarging aneurysms could thus be caused by direct irritation of the third nerve. Compressive cavernous sinus lesions may also spare the pupil because they often preferentially involve only the superior division of the oculomotor nerve that carries no pupillomotor fibers, or the superior aspect of the nerve anterior to the point where the pupillomotor fibers descend in their course near the inferior oblique muscle. The pupillary “sparing” with anterior cavernous sinus lesions may be more apparent than real, resulting from simultaneous injury of nerve fibers to both the pupillary sphincter and dilator, causing a midposition, fixed pupil, or resulting from aberrant regeneration (see below). Ikeda et al described a patient with a painful, “severe” third nerve palsy with normal pupils due to a cavernous sinus aneurysm. Lesions near the posterior clinoid process may for some time affect only the third nerve as it pierces the dura (e.g., breast and prostatic carcinoma). Medial lesions in the cavernous sinus, such as a carotid artery aneurysm, may affect only the oculomotor nerves, but spare the more laterally located ophthalmic branch of the trigeminal nerve, resulting in painless ophthalmoplegia.

### Isolated Third Nerve Palsy Due to an Orbital Lesion

Lesions within the orbit that produce third nerve dysfunction usually produce other oculomotor dysfunction as well as optic neuropathy and proptosis. Isolated involvement of the muscles innervated by either the superior or the inferior oculomotor branch has classically been localized to an orbital process (often trauma, tumor, or infection) or a pheno-cavernous lesion. However, as noted above, the functional division of the third nerve is present, probably even at the fascicular level, and a divisional pattern may occur from damage anywhere along the course of the nerve. Superior division or inferior division third nerve paresis may occur with subarachnoid lesions, and isolated superior division paresis has been described with a superior cerebellar-posterior cerebral artery junction aneurysm that compressed and flattened the interpeduncular third nerve from below. Superior branch palsy has also been described with basilar artery aneurysm, posterior communicating artery aneurysm, intracavernous carotid aneurysm, migraine, diabetes, lymphoma, sphenoidal abscess, sphenoid sinusitis, frontal sinus mucocele, viral illness, and meningitis, as well as after craniotomy. Even ophthalmoplegic migraine may cause recurrent paroxysmal superior division oculomotor palsy. Isolated superior division-like paresis may be mimicked by myasthenia gravis. Isolated inferior division involvement has occurred with trauma, mesencephalic infarction and tumor, basilar artery aneurysm, parasellar tumors (e.g., meningioma, schwannoma), viral illness, orbital dural arteriovenous malformation, as part of a more generalized vasculitic or demyelinating neuropathy, and in association with elevated antiglutamate decarboxylase and anti-GM1 (monosialotetrahexosylganglioside) antibodies. Inferior division involvement with tumors may be pupil-sparing, perhaps because of insidious tumor growth sparing pressure-resistant pupillomotor fibers.

Partial or complete third nerve palsy may rarely follow dental anesthesia, presumably due to inadvertent injection of an anesthetic agent into the inferior dental artery or superior alveolar artery with subsequent retrograde flow into the maxillary, middle meningeal, and finally the lacrimal branch of the ophthalmic artery.

For clinical purposes, isolated third nerve palsy may be divided into three types: types 4A to 4C.
Acquired Isolated Third Nerve Palsy with a Normal Pupillary Sphincter with Completely Palsied Extraocular Muscles (Type 4A Third Nerve Palsy)

Third nerve palsy with a normal pupillary sphincter and completely palsied extraocular muscles is almost never due to an intracranial aneurysm. A single patient has, however, been described in whom a painless, pupil-sparing but otherwise complete, third nerve palsy was the only sign of an aneurysm arising from the basilar artery.46 A similar painful third nerve palsy has been described with an aneurysm in the cavernous sinus,42 and pupillary sparing may rarely occur with pituitary adenoma. This type of third nerve palsy is most commonly caused by ischemia, especially associated with diabetes mellitus. In a retrospective review of 34 consecutive cases of isolated atraumatic third nerve palsies, diabetes mellitus was the most common etiology accounting for 46% of the cases.50 Ischemic third nerve palsy may also occur with giant cell arteritis50,51 and systemic lupus erythematosus. Pupil-sparing third nerve palsy has also been reported with sildenafil citrate (Viagra®; Pfizer Pharmaceuticals, New York, NY)52 and cocaine use.53 Significant risk factors for ischemic oculomotor nerve palsies include diabetes, left ventricular hypertrophy, and elevated hematocrit.54 Obesity, hypertension, and smoking are also probable risk factors. Ischemic damage to the trigeminal fibers in the oculomotor nerve may be the source of pain in ischemic–diabetic third nerve palsies.55

Ischemic lesions of the oculomotor nerve often spare the pupil because the lesion is confined to the core of the nerve and does not affect peripherally situated pupillomotor fibers. The pupil may, however, be involved in diabetic oculomotor palsies;6; diabetes may even cause a superior branch palsy of the oculomotor nerve.57 Pupil sparing has been documented in 62 to 86% of third nerve palsies due to ischemia.58 In a prospective study of 26 consecutive patients with diabetes-associated third nerve palsies, internal ophthalmoplegia occurred in 10 patients (38%).58 The size of anisocoria was ≤1 mm in most patients. Only two patients had anisocoria >2.0 mm and it was never greater than 2.5 mm. No patient had a fully dilated unreactive pupil. The author concluded that pupil involvement in patients with diabetes-associated third nerve palsy occurs more often than has previously been recognized (14 to 32% in other studies), although the degree of anisocoria in any patient is usually 1 mm or less. When commenting on this study, Trobe49 stated that “we can presume that all patients who have oculomotor nerve palsies with anisocoria of greater than 2.0 mm are outliers for the diagnosis of ischemia.” Shih et al59 noted that 28.6% of diabetic ischemic third nerve palsy patients had pupil involvement.

Postmortem examinations in three diabetic patients have demonstrated pathologic changes in the subarachnoid or cavernous sinus portion of the nerves. Ischemic third nerve palsy with pupillary sparing has, however, also been reported due to fascicular damage with mesencephalic infarcts documented on MRI.11,50 Keane and Ahmedi, however, noted that most diabetic third nerve palsies are peripheral.61 In their MRI study of 49 diabetic patients with isolated, unilateral third nerve palsies, only one was found to have a brainstem infarct. Of eight diabetics with midbrain infarcts and third nerve palsies, seven had other central nervous system findings, and five had bilateral third nerve palsies.

In a prospective study of 16 patients with ischemic third nerve palsies, 11 (69%) had progression of ophthalmoplegia with a median time between reported onset and peak severity of ophthalmoplegia of 10 days.62 All patients with ischemic third nerve palsy improve within 4 to 12 weeks of onset of symptoms.63 Sanders et al64 retrospectively studied 55 patients with vasculopathic third nerve palsy. Of these, 42 (76%) had normal pupillary function. Of the 42 patients, 23 (55%) demonstrated an incomplete extraocular muscle palsy, defined as partially reduced ductions affecting all third nerve innervated extraocular muscles and levator (diffuse pattern) or partially reduced ductions that involved only some third nerve innervated muscles and levator (focal pattern). Twenty (87%) of these 23 patients showed a diffuse pattern or paresis; only 3 (13%) showed a focal pattern of paresis, one that affected only the superior rectus and levator muscles (superior division weakness). Based on their series, the authors noted that most patients with extraocular muscle and levator involvement in pupil-sparing, incomplete third nerve palsies of vasculopathic origin have a diffuse pattern of paresis. However, on literature review, pupil-sparing third nerve palsy of aneurysmal origin usually have a focal pattern of paresis.64

Adults who develop type 4A third nerve palsy (Table 1) do not need angiography.47,65 A MRI scan need not be performed initially, as the yield for detecting a compressive lesion is very low, especially if the third nerve palsy resolves over time. Neuroimaging should be performed in patients with no vasculopathic risk factors or in patients who do not improve by 12 weeks of follow-up. Patients with type 4A third nerve palsy should be observed at 24- to 48-hour intervals during the first week because some patients with aneurysms may develop delayed pupil involvement. Patients who develop pupil involvement should be reevaluated (see below). Vasculopathic risk factors, especially diabetes mellitus, hypertension, and increased cholesterol, should be sought and controlled. Patients over the age of 55 years, especially those with other symptoms suggestive of giant cell arteritis (e.g., headache, jaw or tongue claudication, polymyalgia rheumatica symptoms), should have
a sedimention rate determination. Temporal artery biopsy should be performed if the sedimentation rate is elevated or other systemic symptoms are present. Myasthenia gravis may rarely mimic this type of third nerve palsy, so an evaluation (e.g., Tensilon® or Prostigmin® test [both Valeant Pharmaceuticals International, Aliso Viejo, CA], antiacetylcholine antibodies, etc.) should be considered, primarily in patients with fluctuating or fatiguing ptosis or ophthalmoplegia. If the complete, pupil-spared third nerve palsy improves following a period of observation, no neuroimaging is required. Some authors recommend noninvasive vascular studies (MRI with MR angiography [MRA] or CT angiography) in all patients with third nerve palsy—regardless of whether they have diabetes or any other systemic vasculopathy—with the one exception being patients with an otherwise complete third nerve palsy (i.e., complete ptosis, no adduction, no depression, no elevation), but normally reactive, isocoric pupil.

Acquired Isolated Third Nerve Palsy with a Normal Pupillary Sphincter and Incomplete Palsied Extraocular Muscles (Type 4B Third Nerve Palsy)

Patients with an incomplete motor third nerve palsy with pupillary sparing require an MRI scan to rule out a mass lesion. If the MRI scan is normal, cerebral angiography should be considered to investigate the presence of an aneurysm, dural-cavernous sinus fistula, or high-grade carotid stenosis. Three-dimensional time-of-flight (3D TOF) MRA or CT angiography (CTA) may well reveal an aneurysm or other vascular malformation, and may eventually take the place of arteriography. However, at this time, cerebral angiography is the gold standard for the diagnosis of cerebral aneurysms. Although MRA may be able to detect up to 95% of cerebral aneurysms that will bleed, it cannot exclude aneurysm as the etiology of a pupil-involved third nerve palsy. Jacobson and Trobe addressed whether or not MRA was adequate for evaluating for aneurysms in patients with third nerve palsy. They noted that in 46 well-documented aneurysms of the posterior communicating artery causing third nerve palsy, the aneurysm diameters ranged from 3 to 17 mm (median 8 mm); 42 of these (91.3%) measured ≥ 5 mm, and 4 (8.7%) measured < 5 mm. They then investigated how sensitive MRA is in detecting aneurysms, and found that MRA detected 64 (97%) of 66 aneurysms ≥ 5 mm in diameter, but only 15 (53.6%) of 28 aneurysms < 5 mm in diameter. The relationship between aneurysm size and risk of rupture was then assessed. Among 115 aneurysms ≥ 5 mm, 15 (13.3%) ruptured; none of the 40 aneurysms with a diameter of < 5 mm ruptured. Combining these data, the authors estimated that properly performed MRA will overlook only 1.5% of aneurysms that cause third nerve palsy and that will go on to rupture during the subsequent 8 years if untreated. The authors believe that MRA may assume an important role in the evaluation of patients with isolated third nerve palsy. When MRA is properly performed and interpreted, the risk of overlooking an aneurysm likely to rupture is nearly equal to the aggregate risk of stroke, myocardial infarction, or death associated with catheter angiography. Because of the potentially drastic consequences of overlooking an aneurysm, however, the authors believe that MRA should be considered the definitive screening test only in patients with a relatively low likelihood of harboring an aneurysm or relatively high likelihood of suffering a complication during catheter angiography (e.g., age > 70 years, symptomatic atherosclerotic cardiovascular disease, significant cardiovascular or renal disease, Ehlers–Danlos syndrome). In patients with type 4B third nerve palsy (“pupil-sparing incomplete third nerve palsy”) (plus patient age ≥ 40 years and vasculopathic factors present), these authors recommend MRI followed by MRA if MRI does not disclose a non-aneurysmal cause. Catheter angiography is recommended if (1) worsening of extraocular muscle or iris spinchter impairment continues beyond 14 days; (2) iris spinchter impairment progresses to anisocoria > 1 mm, (3) no recovery of function occurs within 12 weeks; or (4) signs of aberrant regeneration develop.

Pupil involvement is not diagnostic of aneurysmal compression, and up to 38% of presumed ischemic third nerve palsies involve the pupil. Thus, a certain number of negative cerebral angiograms would be expected in the evaluation of pupil involved third nerve palsy. The 1 to 2% risk of catheter angiography must be considered, however, in the decision for angiography. MRI and angiography are especially warranted for superior division third nerve palsy. Myasthenia gravis may rarely mimic a superior division third nerve palsy, so a Tensilon test should be performed in these cases. If a patient with a partial third nerve palsy has signs of meningeal irritation, other cranial nerve palsies, or signs of more diffuse meningeal involvement (e.g., radiculopathies) then a spinal tap to investigate infectious, inflammatory, or neoplastic meningitis should be performed. In cases of presumed or suspected subarachnoid hemorrhage, a CT may be the preferred initial imaging study followed by cerebral angiography.

Isolated Acquired Third Nerve Palsy with Subnormal Pupillary Sphincter Dysfunction and Partial or Complete Extraocular Muscle Palsies (Type 4C Third Nerve Palsy)

Patients with a “relative pupil sparing” third nerve palsy should have an MRI scan to rule out the possibility of a compressive lesion. Such patients should also have a CT scan if a subarachnoid hemorrhage is suspected and a
subsequent cerebral angiogram if the MRI scan is negative because of the possibility of a cerebral aneurysm. Cullom et al. published a small prospective study of 10 patients with “relative pupillary sparing” third nerve palsy, and none of the patients demonstrated aneurysms. These authors suggested that the prevalence of aneurysm in patients with palsies of this type may be low enough to preclude routine angiography in this group. This report and subsequent recommendation was, however, based on an inadequate patient sample. Jacobson reported 24 patients with relative pupil-sparing third nerve palsy and found that 10 had nerve infarction, eight had parasellar tumors, two had intracavernous carotid aneurysms, one had leptomeningeal carcinomatosis, one had Tolosa–Hunt syndrome, one had oculomotor neurilemmoma, and one had primary ocular neuromyotonia. Also, others have reported internal carotid, posterior communicating, and basilar artery aneurysms in isolated third nerve palsy with relative pupillary sparing. Thus, cerebral angiography may still be warranted if the MRI scan is negative. Because 10 to 38% of patients with ischemic third nerve palsies have pupillary dysfunction, using these guidelines, there will be a certain percentage of normal angiograms.

In the Jacobson and Trobe study discussed above, in patients with the iris sphincter partially impaired, but with the extraocular muscle function totally impaired (relative pupil-sparing complete third nerve palsy) plus patient age ≥ 40 and vascular risk factors present, the authors recommend MRI followed by MRA if MRI does not show a nonaneurysmal cause. Catheter angiography may still be required in these patients.

In evaluating these patients, one must be cautious to avoid mistaking “pseudo” pupil sparing, due to aberrant regeneration (below) or coexistent Horner’s syndrome, from true relative pupil sparing. In both of these conditions, a compressive lesion is likely localized in the cavernous sinus. Thus, pupil sparing or pseudo pupil sparing third nerve palsies may occur not only with extraaxial ischemic lesions, but also in intraxial (midbrain) lesions, in a small proportion of subarachnoid compressive lesions, and in a high proportion of cavernous sinus compressive lesions.

Complete external and internal third nerve palsies occurring in isolation are often due to compressive lesions or meningeal infiltration; thus, an MRI scan is initially warranted. If this study is negative, a cerebral angiogram is necessary to investigate aneurysm or dural-cavernous sinus fistula. If meningeal signs are present, spinal fluid evaluation is warranted. A CT scan should be performed for suspected subarachnoid hemorrhage. In patients with totally impaired iris sphincter function and impairment of extraocular muscle function (pupil-blown third nerve palsy), Jacobson and Trobe recommend MRI followed by catheter angiography if the MRI scan does not disclose a nonaneurysmal cause. A fully dilated and nonreactive pupil occurs in up to 71% of patients with aneurysmal compression and third nerve palsy. Aneurysms impair the pupil in 96% of third nerve palsies and the remaining 4% in which the pupil is spared have only partial third nerve palsy.

**Progressive or Unresolved Third Nerve Palsy (Type 5 Third Nerve Palsy)**

Patients with third nerve palsy that worsen after the acute stage (>2 weeks) or who develop new neurologic findings are considered to have progressive third nerve palsy. Patients without resolution of third nerve palsy after 12 to 16 weeks are considered unresolved. These patients require MRI and MRA or standard angiography. If signs of meningeal irritation or multiple cranial nerve palsies are present, lumbar puncture (LP) is indicated.

**Third Nerve Palsy Associated with Signs of Aberrant Regeneration (Type 6)**

Months to years after the occurrence of a third nerve palsy, clinical findings of aberrant regeneration of the third nerve may be noted. They include elevation of the lid on downward gaze (pseudo-von Graefe phenomenon) or on adduction, but lid depression during abduction. Other findings include limitation of elevation and depression of the eye with occasional eyeball retraction on attempted vertical gaze, adduction of the eye on attempted elevation or depression, and suppression of the vertical phase of the optokinetic response. The pupil may be in a miotic or mid-dilated position; it may be fixed to light, but may respond to near (near-light dissociation) or constrict on adduction or down-gaze. Normal pupillary function has been described in a patient with aberrant third nerve palsy due to a posterior communicating artery aneurysm.

Aberrant regeneration may be seen after third nerve palsy due to congenital causes, trauma, aneurysm, migraine, and syphilis, but it is very rarely caused by ischemic neuropathy. A single case of aberrant regeneration has been described after an ischemic stroke affecting the third nerve fascicle in the cerebral peduncle. Misdirection of regenerating nerve fibers is likely the cause, but it has been postulated that the syndrome may be due to ephaptic neuron transmission of impulses or from chromatolysis-induced reorganization of third nerve nuclear synapses. Ephaptic transmission would explain the transient third nerve misdirection described with ophthalmoplegic migraine, temporal arteritis, pituitary apoplexy, and non-Hodgkin’s lymphoma. Long-standing lesions, such as meningiomas of the cavernous sinus, trigeminal neuromas, large
aneurysms, and pituitary tumors, may present as primary aberrant regeneration of the third nerve without a history of previous third nerve palsy. Primary aberrant regeneration may rarely occur with extracavernous lesions, such as neurilemmoma, meningioma, asymmetric mammary body, or intradural aneurysm. Bilateral primary aberrant regeneration may also occur with abetalipoproteinemia (Bassen–Kornzweig syndrome). On rare occasions, the pseudo-von Graefe phenomenon may develop contralateral to a regenerating paretic third nerve.

All patients with nontraumatic third nerve palsy with aberrant regeneration (type 5) require MRI and MRA (and possible angiography) to investigate the possibility of a compressive lesion. This is especially true if signs of aberrance develop in a patient with presumed “ischemic” third nerve palsy or in patients with primary aberrant regeneration.

**ANATOMY OF CRANIAL NERVE IV (THE TROCHLEAR NERVE)**

The trochlear nucleus lies caudal to the oculomotor nuclear group, dorsal to the medial longitudinal fasciculus, and at the level of the inferior colliculus, just ventrolateral to the cerebral aqueduct. The nerve fascicles course posteroinferiorly around the aqueduct to decussate in the dorsal midbrain in the anterior medullary velum; they then emerge from the brainstem near the dorsal midline, immediately below the inferior colliculi. The cisternal segment then runs anteriorly over the lateral aspect of the brainstem, successively traversing the quadrigeminal, ambient, crural, and ponsomencephalic cisterns; the cisternal part of the nerve is closely related to the tentorium cerebelli. After traveling on the undersurface of the tentorial edge, it pierces the dura at a point slightly below the point of entry of the oculomotor nerve into the cavernous sinus along the lateral aspect of the clivus just below the petroclinoid ligament. Within the lateral wall of the cavernous sinus, the trochlear nerve lies below the oculomotor nerve and above the ophthalmic division of the trigeminal nerve, with which it shares a connective tissue sheath. The trochlear nerve enters the orbit through the superior orbital fissure and innervates the superior oblique muscle.

**CLINICAL FEATURES OF FOURTH NERVE PALSIES**

Fourth cranial nerve palsies may cause:

1. Incomitant hypertropia demonstrated with the three-step maneuver. The hypertropia increases on head tilt toward the paralyzed side (positive Bielschowsky’s test). Usually the unaffected eye is fixating and the hypertropia occurs in the involved eye. Hypotropia may occur in the normal eye if the affected eye is fixating. The hypertropia is usually most prominent in the field of gaze of the involved superior oblique muscle, especially in cases of acute or recent onset. The hypertropia may also be most prominent in the field of gaze of the ipsilateral overacting inferior oblique muscle in subacute or chronic cases. In palsies of longer duration, the hypertropia may be relatively equal in the various gaze positions (spread of comitance).

2. Underaction of the ipsilateral superior oblique muscle, overaction of the ipsilateral inferior oblique muscle, or overaction of the contralateral superior oblique muscle as revealed by duction testing.

3. Pseudo-overaction of the superior oblique in the uninvolved eye. This may occur with spread of comitance. Secondary contracture of the superior rectus muscle in the involved eye may cause hypertropia involving the entire lower field of gaze. In a patient with a superior oblique muscle paralysis who habitually fixates with the paretic eye and in whom overaction of the ipsilateral inferior oblique muscle has developed, less than the normal amount of innervation will be required when the patient looks up and to the contralateral side. Because the innervation flowing to the opposite superior rectus muscle is “determined” by the overacting ipsilateral inferior oblique muscle (Hering’s law), the opposite superior rectus muscle will seem paretic (inhibitory palsy of the contralateral antagonist). In these cases, the head tilt test will correctly determine which of the two eyes is paretic.

4. Excyclotropia due to loss of incyclotorsion function of the superior oblique muscle. This torsion may be evident on fundus exam and can be measured using double Maddox rod testing. The excyclotropia is usually symptomatic in acquired cases, but is often asymptomatic in congenital cases.

5. An anomalous head tilt to eliminate the hypertropia or less commonly the cycloptropia. This head tilt is present in ~70% of patients and is usually away from the involved side, but may be paradoxical (toward the involved side) in ~3%.

It is important to differentiate patients with decompensation of a congenital fourth nerve palsy from those with an acquired fourth nerve palsy. In patients with congenital fourth nerve palsies:

1. Old photos may show a long-standing head tilt.
2. Patients usually are noted to have cyclotropia on examination, but often do not complain of cyclotropia (subjective image tilting) as do some patients with acquired fourth nerve palsies.
3. Large vertical fusional amplitudes (>6 to 8 prism diopters) in primary gaze are characteristic of congenital cases.
4. Facial asymmetry (hypoplasia on side of head turn) suggests a congenital lesion.

Six types of fourth nerve palsy are defined in Table 2.

**Type 2: Fourth Nerve Palsy Due to Trauma**

Multiple retrospective studies of traumatic (type 2) fourth nerve palsy have recommended that isolated, traumatic, unilateral, or bilateral fourth nerve palsies do not require additional neuroimaging or further evaluation.\(^{82,83}\) Fourth nerve palsy after mild head trauma has been observed in association with an underlying asymptomatic basal intracranial tumor in at least three reports.\(^{84–86}\) Neetens reported three such cases, but two cases had other neuroophthalmologic signs as well.\(^{86}\) Although uncommon, neuroimaging may be warranted in patients with fourth nerve palsy after minimal or trivial head trauma to exclude a mass lesion.

**Type 3: Congenital Fourth Nerve Palsies**

Clearly congenital unilateral or bilateral fourth nerve palsies (type 3) are not associated with intracranial lesions in isolation, and therefore do not require further diagnostic evaluation such as neuroimaging studies.

**Type 4: Vasculopathic Fourth Nerve Palsies**

Vasculopathic fourth nerve palsies (type 4) often resolve spontaneously within 4 to 6 months. Rush reported a recovery rate for fourth nerve palsy of 53.5\% in 172 nonselected cases, and a higher recovery rate of 71\% in 166 patients with diabetes mellitus, hypertension, or atherosclerosis.\(^{87}\) Another report by Ksiazek et al described improvement in 90\% of 39 patients with microvascular and idiopathic fourth nerve palsies within 6 months.\(^{88}\) Vasculopathic fourth nerve palsies usually improve within a few months,\(^{59,87,89,90}\) and patients with progressive or unresolved fourth nerve palsies, or with new neurologic signs or symptoms, should have neuroimaging.\(^{86,87,91,92}\) Patients with spontaneously resolving palsies do not require any further neuroimaging. It is recommended that elderly patients who present with headache, scalp tenderness, jaw claudication, or visual loss undergo an appropriate evaluation for giant cell arteritis, including an erythrocyte sedimentation rate and a temporal artery biopsy. There is insufficient evidence to recommend evaluation for giant cell arteritis in every elderly patient with motility testing suggesting an isolated fourth nerve palsy.

**Evaluation of Nonvasculopathic Fourth Nerve Palsy (Type 5)**

Nonvasculopathic fourth nerve palsy (type 5) may be observed for improvement over the next 6 to 8 weeks. Patients with resolution of symptoms and signs do not require further evaluation. Patients with progression or lack of resolution should undergo neuroimaging (preferably MRI). Myasthenia gravis may mimic fourth nerve...
palsy, and patients with variable or fatigable motility findings and/or ptosis should be evaluated for myasthenia gravis.86

Testing for vasculopathic risk factors in type 4 or type 5 fourth nerve palsy should be considered, even in the absence of a history of previous diabetes or hypertension. Green et al92 reported an isolated third nerve palsy as the initial clinical manifestation of diabetes in almost half of 25 patients. Shrader and Schlezinger93 reported that almost 50% of diabetic sixth nerve palsies were the presenting clinical manifestation of the disease. The results of these studies concerning vasculopathic third and sixth nerve palsies may well be applicable to vasculopathic fourth nerve palsy.

Lesions of the subarachnoid space are rarely associated with an isolated fourth nerve palsy. Patients with subarachnoid space lesions usually have associated signs and symptoms including headache, stiff neck, and other cranial neuropathies. Neuroimaging (usually MRI) should be directed to the brainstem and subarachnoid space. CT should be considered in cases of acute trauma, to evaluate bone lesions, or in the evaluation of acute vascular processes (e.g., subarachnoid hemorrhage). LP following negative neuroimaging should be considered in these cases.

Younger patients, or those without vasculopathic risk factors (type 5), may require initial neuroimaging, but the data suggest that observation for spontaneous improvement may be sufficient. Isolated, idiopathic fourth nerve palsies very rarely have been found to have an underlying etiology after prolonged follow-up, and most resolve spontaneously within several weeks to months.88,94,95 Two retrospective case series with follow-up > 6 months described the prognosis of isolated, idiopathic fourth nerve palsy. Coppeto et al94 reported that 12 of 15 cases had resolved by 4 months after a mean follow-up of 5.5 years. Nemet et al95 described 13 cases, with a follow-up ranging from 4 to 7 years, and all had resolved by 10 weeks. None of the patients in either series developed new neurologic disease over an extensive follow-up period. Although type 5 patients who improve may not require neuroimaging, the clinical certainty of such a recommendation is not sufficiently strong to obviate the need for neuroimaging in these nonvasculopathic patients. Patients without improvement after 2 months, however, should have consideration for neuroimaging. Some reports have described aneurysm as an extremely rare cause for isolated fourth nerve palsy,87,90,91,96 and cerebral angiography is not recommended unless an aneurysm is suggested by other neuroimaging studies. Collins et al and Agostinis et al reported isolated fourth nerve palsy due to superior cerebellar aneurysms, but both patients described headaches.90,96 In these cases, neuroimaging studies confirmed the presence of the aneurysm before angiography. There is insufficient data to make a comment on the usefulness of MRA in fourth nerve palsy.

Although MRI scans are generally felt to be more sensitive and specific than CT scans in the evaluation of cranial neuropathies, no conclusive evidence demonstrates an increased yield from performing an MRI scan rather than a CT scan for the specific evaluation of fourth nerve palsy. Richards et al97 reported an etiologic diagnosis in 69 of 144 (48%) fourth nerve palsies using MRI, and in 289 of 684 (42%) cases using CT. These authors felt that “multiplanar CT may be a sufficient noninvasive study, especially when clinical suspicion is high . . . (or) in patients with other neurologic findings . . . .”97 Nevertheless, MRI is the study of choice for patients with fourth nerve palsy.

Several cases have been reported in the literature documenting intracranial lesions in patients with fourth nerve palsy. Of 86 patients reviewed, only 5 (5.8%) did not have other neurologic signs or symptoms and thus would be considered truly isolated by our criteria. One developed other neurologic signs after a short follow-up period, and in the remaining four patients, persistence or progression of symptoms would have eventually resulted in a neuroimaging study. Of the remaining 81 patients, six had headache or pain (7.0%), 31 had other neurologic signs (36%), and the clinical information was insufficient to determine if the fourth nerve palsy was truly isolated in 44 patients (52%). Keane reported intracranial tumor as an etiology in 12 of 95 unilateral cases, but all 12 (100%) had other neuroophthalmic signs; none of 81 isolated fourth nerve palsies later reported by Keane had an intracranial tumor.98 This would suggest that the yield for evaluation of an isolated fourth nerve palsy is low.

All patients with progressive fourth nerve palsy (type 6) should undergo neuroimaging (preferably MRI). LP should be considered if neuroimaging is normal or if there are signs or symptoms of meningeal irritation.

**ANATOMY OF CRANIAL NERVE VI (THE ABDUCENS NERVE)**

The paired abducens nuclei are located in the dorsal lower portion of the pons, separated from the floor of the fourth ventricle by the genu of the facial nerve (facial colliculus). The nucleus contains motor neurons for the lateral rectus muscle and interneurons traveling via the medial longitudinal fasciculus (MLF) to the contralateral medial rectus subnucleus of the third nerve. The sixth nerve nucleus thus contains all the neurons responsible for horizontal conjugate gaze. The nerve fascicle leaves the nucleus and travels within the substance of the pontine tegmentum, adjacent to the medial lemniscus and the corticospinal tract. The sixth nerve leaves the brainstem in the horizontal sulcus between the pons and
Sixth nerve palsy is a clinical condition characterized by weakness or paralysis of the sixth cranial nerve, also known as the abducens nerve. This nerve is responsible for controlling the movement of the eye to the opposite side of the head, primarily for the purpose of binocular vision. The anatomy of the sixth nerve palsy involves multiple aspects of neural and vascular territories.

**SIXTH NERVE PALSY**

Based upon this topographic anatomy, sixth nerve palsy may be divided into isolated sixth nerve palsy and nonisolated sixth nerve palsy. The criteria for the diagnosis of an isolated sixth nerve palsy are listed in Table 3.

We define six types of sixth nerve palsy in Table 4. These types help to differentiate etiology and guide the management of sixth nerve palsy.

### Recommendations for the Evaluation of Sixth Nerve Palsy

1. **Nonisolated sixth nerve palsy (type 1)** should undergo neuroimaging and further evaluation. Special attention should be directed to areas suggested topographically by the associated neurologic signs or symptoms.

2. **Traumatic sixth nerve palsy (type 2)** should undergo the appropriate acute neuroimaging (CT scanning) as indicated by the trauma and associated neurologic signs and symptoms. In acute traumatic sixth nerve palsy, failure to recover by 6 months after onset was associated independently with inability to abduct past midline at presentation and bilaterality.

3. **Congenital sixth nerve palsies (type 3)** are rare and there is insufficient data to make a strong recommendation for the management of congenital isolated sixth nerve palsy from our review of the literature. Nevertheless, if the sixth nerve palsy can be clearly demonstrated to be congenital in origin, additional neuroimaging is not generally required. Transient sixth nerve palsy may occur following birth trauma in newborns. Galbraith reported the incidence of sixth nerve palsy in a group of 6886 neonates as being 0.4%. All of these sixth nerve palsies (type 3) resolved within 6 weeks; it is recommended that imaging be deferred in these patients. The incidence of sixth nerve palsy increased with “complexity of
instrumentation,” with 0% prevalence for cesarean section, 0.1% prevalence for spontaneous vaginal delivery, 2.4% prevalence for forceps delivery, and a 3.2% prevalence for vacuum extraction. Leung\textsuperscript{101} reported three cases of right sixth nerve palsy after vaginal delivery that all resolved after 4 to 12 weeks. Observation for improvement is a reasonable approach in these cases.  

4. Isolated vasculopathic sixth nerve palsy (type 4) may be observed (without neuroimaging) for improvement for 4 to 12 weeks. Rush and Young\textsuperscript{87} reported a recovery rate of 49.6% in 419 nonselected sixth nerve palsy cases, and a higher rate of 71% in 419 patients with diabetes mellitus, hypertension, or atherosclerosis. Some authors have recommended observing vasculopathic isolated sixth nerve palsy beyond a 3-month interval of recovery if the esotropia and the abduction deficit were decreasing.\textsuperscript{102} Elderly patients who present with an isolated sixth nerve palsy and headache, scalp tenderness, jaw claudication, or visual loss should undergo an appropriate evaluation for giant cell arteritis. An erythrocyte sedimentation rate should be determined, and when clinically indicated, a temporal artery biopsy. Patients with progression or lack of improvement (type 6) should undergo neuroimaging. It should be noted that early progression of paresis over one week in vasculopathic sixth nerve palsy is not uncommon.\textsuperscript{103} In one study, only 2 of 35 patients with ischemic sixth nerve palsy had initial complete abduction deficits.\textsuperscript{103} Of 33 patients with initial incomplete deficits, 18 (54%) showed progression over a 1-week period. Progression over the first week after onset is not considered to be a sign of nonvasculopathic sixth nerve palsy.  

5. Nonvasculopathic sixth nerve palsy (type 5) should undergo neuroimaging. Younger patients, or those without vasculopathic risk factors (type 5), could also undergo a more extensive evaluation, including a fasting blood glucose, complete blood cell count, and blood pressure check for underlying vasculopathy. Other testing, including neuroimaging (MRI) and if necessary LP, are recommended. Type 5 sixth nerve palsies have a significant (27%) chance of harboring an underlying malignant neoplasm.\textsuperscript{104} Evaluation for myasthenia gravis should also be considered in these patients.  

6. Testing for vasculopathic risk factors in type 4 or type 5 sixth nerve palsy should be performed, even in the absence of a previous history of diabetes or hypertension.\textsuperscript{102,105,106} Oculomotor cranial neuropathies may be the presenting or only sign of underlying vasculopathy in these patients.  

7. Patients with progressive or unresolved sixth nerve palsy (type 6), or patients with new neurologic signs or symptoms, should undergo neuroimaging.\textsuperscript{102,104,105,107} Progressive, or unresolved sixth nerve palsy, should probably have neuroimaging. Galetta and Smith described 13 chronic sixth nerve palsies.\textsuperscript{106} Of these, four were idiopathic, four were due to tumor, two were traumatic, one was due to postspinal anesthesia, one was due to temporal arteritis, and one was due to an intracavernous aneurysm. In their study, chronic was defined as a sixth nerve palsy lasting 6 months or longer. Savino et al\textsuperscript{105} reviewed 38 patients with chronic sixth nerve palsy; 14 (37%) were discovered to have an intracranial lesion. These authors specifically recommended neuroradiologic investigation at onset in any patient with a history of carcinoma.  

Moster et al\textsuperscript{107} commented on the lack of truly isolated sixth nerve palsy reported in the literature. Most reports do not separate unilateral from bilateral sixth nerve palsy, or isolated sixth nerve palsy from those associated with other neurologic or cranial nerve defects.\textsuperscript{104} Our review of the literature on sixth nerve palsy revealed 31 case reports and case series describing 237 patients with presumed isolated sixth nerve palsy.\textsuperscript{109} Of these 237 patients, 31 were traumatic, none were congenital, 60 were vasculopathic, 47 were “idiopathic,” and the remainder had several miscellaneous etiologies (seven post-LP, 19 multiple sclerosis, two postimmunizations, five “infectious,” five aneurysms, one sarcoid, six “presumed inflammation,” one orbital amyloidosis, and one diverticulum of the cavernous sinus). Fifty-two cases were the result of tumors (including chordomas, chondrosarcomas, meningiomas, cylindroma, lymphomatous meningitis, schwannomas, nasopharyngeal carcinoma, metastases, trigeminal neurilemoma, pontine glioma, pituitary adenomas, and miscellaneous tumors). The remaining sixth nerve palsies in the literature review were associated with other neurologic signs or symptoms, such as headache, tinnitus, disk edema, nystagmus, and so on, or there was insufficient clinical data in the report to determine if the sixth nerve palsy was truly isolated by the criteria given in Table 3.  

Sixth nerve palsies that occur after LP, postmyelographic LP, and spinal anesthesia have been reported in the literature. Thorsen\textsuperscript{110} reported 229 cases of sixth nerve palsy after spinal anesthesia and LP. Most of these sixth nerve palsies occurred at the tenth day following LP, were unilateral, associated with headache, and occurred in young patients.\textsuperscript{110,111} These patients may be followed for resolution without imaging.  

Aneurysm is a rare cause of acquired sixth nerve palsy. Rucker\textsuperscript{111} reported 924 cases of sixth nerve palsy and only 3.3% or 31 were due to aneurysm. Rush and Young\textsuperscript{87} described 419 cases of sixth nerve palsy and only 3.6% or 15 were due to aneurysm. Other authors\textsuperscript{112} did not find any cases of aneurysm presenting with an isolated sixth nerve palsy in their series on cerebral aneurysms with ocular involvement and others have
reported similar findings. In a study of 137 patients with sixth nerve palsy, an aneurysm was the etiology in 2% of the cases. Evaluation for aneurysm is not typically recommended in isolated sixth nerve palsy, but aneurysm can cause sixth nerve palsy in patients with signs of subarachnoid hemorrhage, papilledema, or other cranial neuropathies.

REFERENCES

61. Keane JR, Ahmadi J. Most diabetic third nerve palsies are peripheral. Neurology 1998;51:1510
65. Miller NR. Unequal pupils can be seen in diabetic 3rd nerve palsy. Evidence-Based Eye Care 1999;1:40–41