Isolated sixth nerve palsy
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Introduction
This article includes discussion of isolated sixth nerve palsy, abducens nerve palsy, and lateral rectus palsy. The foregoing terms may include synonyms, similar disorders, variations in usage, and abbreviations.

Overview
An isolated sixth nerve palsy may be a harbinger of underlying intracranial disease. Due to its long subarachnoid course, it may be damaged by downward shift of the brainstem as often occurs in increased or decreased intracranial pressure (“false-localizing sixth nerve palsy”). Alternatively, the sixth nerve may be involved in isolation by a compressive lesion in the cavernous sinus or along the clivus (“true-localizing sixth nerve palsy”), and specific attention on neuroimaging should be paid to these areas, especially in chronic or progressive cases. The most common causes of a sixth nerve palsy in an adult include ischemia, head trauma, and compression by a mass lesion, but inflammation, primary demyelination, and intracranial hypotension may also produce a sixth nerve palsy.

Key points
• A deficit in abduction is not always due to a sixth nerve palsy; therefore, patients should be considered to have an “abduction deficit” rather than a “sixth nerve palsy” until a diagnosis is confirmed. Alternative causes of an abduction deficit are medial rectus muscle restriction (as in dysthyroid orbitopathy, myositis, orbital wall fracture), myasthenia gravis, Duane type I retraction syndrome, and convergence spasm.
• A minimal sixth nerve palsy can be present without causing a visible abduction deficit. Therefore, the evaluation of patients reporting diplopia may require testing of ocular alignment using prisms.
• Sixth nerve palsy may be caused by increased or decreased intracranial pressure (“false-localizing palsy”) or by lesions in the pons (nucleus and fascicle), subarachnoid space, clivus, cerebellopontine angle, cavernous sinus, superior orbital fissure, and orbit along the course of the nerve (“true-localizing palsy”).
• Chronic or slowly progressive sixth nerve palsies may reflect life-threatening intracranial disease.

Historical note and terminology
The terms sixth nerve palsy, abducens nerve palsy, and lateral rectus palsy are essentially interchangeable.

Clinical manifestations
Presentation and course
Patients with sixth nerve palsies complain of binocular horizontal diplopia worse in the field of action of the paretic lateral rectus muscle. Examination often reveals an ipsilateral abduction deficit and a primary position esotropia that is worse in gaze toward the paretic muscle. A small hypertropia (less than 2 to 3 prism diopters) may be present in unilateral sixth nerve palsies, its mechanism being unresolved. However, a hypertropia greater than 5 prism diopters indicates a concurrent skew deviation, coexisting third or fourth nerve palsy, or myasthenia gravis.

Lesions of the sixth nerve nucleus cause an ipsilateral gaze palsy (neither eye can move fully ipsilateral to the lesion) rather than an isolated abduction deficit because of damage to the interneurons of the medial longitudinal fasciculus (MLF). Oculocephalic maneuvers and caloric testing will not overcome a gaze palsy caused by a nuclear sixth nerve lesion. Damage to the paramedian pontine reticular formation (PPRF) will cause a supranuclear ipsilateral gaze palsy, that is, one that can be overcome by oculocephalic maneuvers and caloric testing. An ipsilateral facial palsy is often present due to the close proximity of the facial nerve fascicles to the sixth nerve nucleus in the pons. Nuclear lesions are often also associated with ataxia. Fascicular lesions may be associated with ataxia, contralateral hemiparesis, or...
contralateral hemisensory loss. Subarachnoid space lesions may result in unilateral or bilateral sixth nerve palsies. Petrous apex lesions may cause facial pain and damage to the fifth, sixth, seventh, and eighth cranial nerves. Gradiento syndrome includes the triad of periocular pain, otitis media, and ipsilateral sixth nerve palsy; it may be treated surgically or with myringotomy and broad spectrum antibiotics (Burston et al 2005). Mastoid or middle ear infection may also lead to transverse sinus thrombosis, especially in children, causing increased intracranial pressure (“otic hydrocephalus”). Manifestations, in addition to sixth nerve palsy, are papilledema, headache, pulsatile tinnitus, fever, ipsilateral hearing loss, and ear pain (Bababeygy et al 2011). Clivus lesions, including chordomas, chondrosarcomas, and metastases, may produce unilateral or bilateral sixth nerve palsies and may be associated with lower cranial neuropathies (Kulkarni et al 2005). Cavernous sinus lesions often damage the third, fourth, first, and second division fifth cranial nerves. There may be damage to the postganglionic oculosympathetic fibers to cause a Horner syndrome. Lesions of the orbit are associated with proptosis, eyelid swelling, conjunctival hyperemia, and impaired eye movements in various directions as well as periocular pain (Brazis 2009).

Neuromyotonia of the sixth nerve presents with limited abduction and transient delayed adduction due to sustained contraction of the lateral rectus after gaze toward the side of the lesioned sixth nerve. A slowly growing compressive lesion or previous external therapeutic radiation of the middle fossa is almost always the cause (Salchow and Wermund 2011).

Any cause of increased or decreased intracranial pressure may result in a unilateral or bilateral sixth nerve palsy. The mechanism is believed to be downward displacement of the brain with tugging on the sixth nerve at its anchor point at the petroclival junction (Dorello's canal) (Kurbanyan and Lessell 2008; Sudhakar et al 2013).

Prognosis and complications

A study of 59 patients with presumed vasculopathic sixth nerve palsy disclosed that 51 (86%) recovered completely within 6 months (Sanders et al 2002). In traumatic sixth nerve palsy, injection of the medial rectus was initially favored as a means of improving recovery. However, in a prospective observational series of 84 patients with acute traumatic sixth nerve palsies, botulinum toxin injections into the medial rectus muscle had no effect on recovery of sixth nerve function (Holmes et al 2001).

Clinical vignette

A 60-year-old man with hypertension and diabetes presented with acute, painless, binocular horizontal diplopia that was worse in right gaze. The patient was maintaining a face turn to the right to avoid diplopia. Testing of ocular movements revealed a moderate abduction deficit of the right eye. On examination of ocular alignment, there was an esotropia of 25 prism diopters in primary position, increasing in right gaze to 40 prism diopters. The remainder of the ophthalmological and neurologic examinations was normal. The patient was diagnosed with an isolated, presumed vasculopathic right sixth nerve palsy. No studies were ordered. The patient experienced complete resolution of the sixth nerve palsy within 4 weeks.

Biological basis

Etiology and pathogenesis


| Table 1. Etiologies of a Sixth Nerve Palsy |

| Nuclear lesions | • Congenital aplasia (Duane, Mobius syndrome) (Pilyugina et al 2007), demyelinating (Uzawa et al 2011), ischemic, neoplastic, traumatic, metabolic (Wernicke disease) processes. |
| Fascicular lesions | • Demyelination (Mitchell et al 2008; Szabo et al 2008; Zadro et al 2008), infarction, neoplasm, hemorrhage (Sherman and Saadatmand 2007; Mallery 2012), or trauma (surgical or nonsurgical) (Palmowski-Wolfe et al 2010). |
Capecitabine, intravitreal bevacizumab, and muscle and interneurons traveling via the medial longitudinal fasciculus to the contralateral third nerve medial rectus.

The sixth nerve originates in a lower pontine nucleus. This nucleus contains motor neurons for the lateral rectus muscle and interneurons traveling via the medial longitudinal fasciculus to the contralateral third nerve medial rectus.
muscle subnucleus. Thus, the nucleus contains all of the neurons responsible for horizontal conjugate gaze. The sixth nerve fascicle leaves the nucleus and travels within the substance of the pontine tegmentum, adjacent to the medial lemniscus, and adjacent to the corticospinal tract. It leaves the brainstem, enters the subarachnoid space (prepontine cistern), courses nearly vertically along the clivus bone, traveling over the petrous apex of the temporal bone where it is tethered at the petroclinoid ligament in Dorello's canal. A study of 12 cadavers found that the sixth nerve was fixed to Dorello's canal in all cases, putting the sixth nerve at risk of traction even from minor head injury (Tubbs et al 2012). The nerve enters the substance of the cavernous sinus lateral to the internal carotid artery and medial to the ophthalmic division of the trigeminal nerve. It enters the orbit through the superior orbital fissure to innervate the lateral rectus muscle.

Epidemiology

Isolated sixth nerve palsy has no gender, age, or racial predilection. Trauma is a common cause in any age group. Children or young adults should be suspected of harboring an intracranial lesion, including brainstem glioma or demyelinating disease. In a review of 16 children younger than 18 years of age (mean=4.5 years) with unilateral isolated sixth nerve palsy, 5 were due to tumor, 4 were idiopathic and recurrent, 3 were post-vaccination or post-viral, 1 was traumatic, 1 was associated with Chiari malformation, 1 was congenital, and 1 was of unknown origin (Dotan et al 2013). Children are subject to a persistently isolated but recurrent sixth nerve palsy that may show enhancement of the subarachnoid portion of the nerve (Knapp and Gottlob 2004; Mahoney and Liu 2009; Okutan et al 2009). A review of the reported cases of recurrent sixth nerve palsy in children described 41 cases, concluding that female gender, left eye involvement, younger age, and recent vaccination were associated with recurrence and that a recurrence was less likely if it did not occur within 1 year of the initial event (Yousuf and Khan 2007).

Older patients are more likely to have a vasculopathic ischemic palsy associated with standard risk factors for small-vessel arteriosclerosis, namely diabetes, hypertension, hyperlipidemia, and smoking (Patel et al 2005).

Differential diagnosis

The differential diagnosis includes restrictive orbitopathies (orbital wall fracture, orbital tumor, idiopathic myositis, thyroid eye disease), myasthenia gravis, and spasm of the near reflex. These entities can usually be distinguished on clinical grounds alone. Patients with restrictive orbital disease usually demonstrate proptosis, chemosis, conjunctival injection, pain with attempted abduction, and positive forced ductions. Myasthenia gravis may mimic any painless, pupil-sparing ophthalmoplegia; other signs of myasthenia such as ptosis, variability, and fatigue are often present. Spasm of the near reflex is associated with a variable esotropia, intermittent pupil constriction, blurred vision (owing to inappropriate accommodation), and a feeling of eye strain. The abduction deficit may resolve when the contralateral eye is occluded.

Diagnostic workup

Sixth nerve palsies may be divided into those that are “isolated” (not accompanied by other pertinent findings) and those that are “non-isolated” (accompanied by other pertinent findings). Bilateral sixth nerve palsies are considered “non-isolated.” They may reflect increased or decreased intracranial pressure or be caused by meningeal or clival lesions in the path of the sixth cranial nerves. Bilateral sixth nerve palsy has also been reported after MDMA (“ecstasy”) abuse (Schroeder and Brieden 2000) and with anti-GQ1b antibody (Sato and Yoshikawa 2001), anti-GM2 antibody (Smyth et al 2011), and rarely with ischemia (Bayrak et al 2006).

Isolated sixth nerve palsies may be traumatic (including surgical), vasculopathic, and idiopathic in origin (Keane and Baloh 1992). Sixth nerve palsies in the setting of head trauma should be evaluated as indicated by the trauma-associated neurologic signs and symptoms. Severe occipitocervical trauma may cause sixth nerve palsies, clival epidural hematoma, and C1-2 instability (Garton et al 2010). Sixth nerve palsy may appear as long as 3 weeks after head trauma due to delayed development of a subdural hematoma (Salunke et al 2012).

Isolated sixth nerve palsy in patients with ample arteriosclerotic risk factors may be presumed to have an ischemic cause and should be observed without neuroimaging for improvement over 4 to 12 weeks. If no improvement has occurred within 12 weeks, or if new findings appear, MRI should be considered. The notion of withholding brain imaging in this setting is controversial; some authorities recommending immediate brain imaging in all new cases of isolated sixth nerve palsy. One group found MRI abnormalities in 27 of 43 patients presenting with an isolated sixth
nerve palsy at a tertiary care center. Those with MRI abnormalities were younger (mean age= 43 years) than those with normal imaging (mean age= 56 years); no further information was given about the patients with abnormal imaging (Bendszus et al 2001). Another publication reported 66 patients who were 50 years of age or older with third, fourth, or sixth cranial mononeuropathies and found 9 with MRI abnormalities, 2 of whom had isolated sixth nerve palsies (1 pituitary apoplexy, 1 brainstem stroke) (Chou et al 2004). A prospective study of 52 patients who were 50 years of age or older and who presented with an acute isolated sixth nerve palsy and underwent high quality MRI with contrast found only 1 patient with a pertinent MRI abnormality—a pontine hemorrhage that resolved spontaneously (Murchison et al 2011).

Because sixth nerve palsy in the elderly may occasionally be caused by giant cell arteritis, other manifestations of this condition (headache, scalp tenderness, jaw claudication, visual loss) should be sought. Even if these manifestations are not found, such patients should undergo testing of erythrocyte sedimentation rate and non-cardiac C-reactive protein and, when clinically indicated, a temporal artery biopsy. Patients with progression or lack of improvement should undergo neuroimaging because these patients may harbor an occult skull base lesion (Savino et al 1982; Galetta and Smith 1989). Attention on imaging should also be directed toward signs of intracranial hypotension (Sudhakar et al 2013). Testing for clinical manifestations of myasthenia gravis should be sought. Even if not evident, patients should undergo ancillary testing in the appropriate setting. The fundus should be examined particularly to rule out papilledema, as sixth nerve palsy may be a sign of increased intracranial pressure.

**Management**

Therapy should be directed at the underlying etiology of the sixth nerve palsy and at palliating the diplopia. All patients with non-isolated sixth nerve palsy should undergo a thorough workup that may include brain imaging, laboratory tests, and lumbar puncture, as appropriate. Patients with isolated sixth nerve palsy should be divided into 2 groups: those that are considered very likely to have a vasculopathic ischemic cause (group 1) and all others (group 2). Group 1 patients may be observed for improvement (see controversy, above). Group 2 patients require a thorough diagnostic workup akin to that for non-isolated palsy.

To alleviate diplopia, one can recommend occlusion of one eye (skin patch, spectacle occluder). Alternating the patch between eyes is reasonable to avoid maceration of the skin but is not necessary as a means of preventing amblyopia in teenagers or adults who are too old to develop it. If the misalignment is not severe, press-on (Fresnel) prisms may provide a reasonable zone of single binocular vision as a temporizing measure. If the sixth nerve palsy persists in a stable form for more than 6 months, and if diplopia is not satisfactorily relieved by prisms or the patient does not wear glasses or does not tolerate long-term prism glasses, surgical realignment of the eyes may be indicated (Holmes and Leske 2002; O'Donnell and Buckley 2006; Yurdakul et al 2011).

**Special considerations**

**Pregnancy**

There are no special issues for sixth nerve palsy in pregnancy except for etiologies for ocular motor neuropathy that may occur in pregnancy (meningioma, pituitary adenoma or apoplexy, idiopathic intracranial hypertension).

**Anesthesia**

Unilateral or bilateral sixth nerve palsy may result from intracranial hypotension from epidural anesthesia complicated by a CSF leak (Sudhakar et al 2013).

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**ICD and OMIM codes**

**ICD codes**

ICD-9:
- Sixth or abducens nerve palsy: 378.54

ICD-10:
- Sixth [abducent] nerve palsy: H49.2

**Profile**

**Age range of presentation**

0-01 month
01-23 months
02-05 years
06-12 years
13-18 years
19-44 years
45-64 years
65+ years

Sex preponderance
male=female

Family history
none

Heredity
none

Population groups selectively affected
none selectively affected

Occupation groups selectively affected
none selectively affected

**Differential diagnosis list**
restrictive orbitopathies
orbital wall fracture
orbital tumor
idiopathic myositis
thyroid eye disease
*myasthenia gravis*
spasm of the near reflex

**Other topics to consider**
Combined third, fourth, and sixth nerve palsies
Diplopia
Isolated fourth nerve palsy
Isolated third nerve palsy