Third Nerve Palsies

What Are the Clinical Features of a Third Cranial Nerve Palsy?

The oculomotor nerve (third cranial nerve) supplies four extraocular muscles (medial, superior and inferior recti, and inferior oblique) as well as the levator of the lid, and contains parasympathetic fibers that supply the sphincter of the pupil and the ciliary body. A complete peripheral third nerve palsy (TNP) thus causes ptosis, a fixed and dilated pupil, and a down (hypotropic) and out (exotropic) resting eye position. Partial TNPs may cause (in combination or isolation) variable ptosis; variable paresis of eye adduction, elevation, and depression; and variable pupillary involvement. In this section, we discuss the localization of TNPs associated with other neurologic signs (nonisolated TNPs) and TNPs without other associated neurologic or neuro-ophthalmologic deficits (isolated TNPs) (Lee, 1999).

Is the TNP Isolated or Nonisolated? Can the TNP Be Localized?

We classify TNPs as either nonisolated or isolated. The isolated TNPs were defined as TNPs 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 TNP group. We define six types of TNP in Table 11–1. The localization of TNP is outlined in Table 11–2. Etiologies of TNPs by localization are outlined in Table 11–3.
Is the TNP Due to a Nuclear Lesion?

Lesions of the third nerve nucleus are rare and often associated with other signs of mesencephalic involvement, especially vertical gaze impairment (Bengel, 1994; Bogoousslavsky, 1994; Chee, 1990; Gaymard, 1990; Nakao, 1998; Saeki, 2000b). Nuclear lesions may be due to infarction, hemorrhage, tumor, infection, or trauma and, thus, should be investigated by magnetic resonance imaging (MRI). Paresis of an isolated muscle innervated by the oculomotor nerve almost always results from a lesion in the orbit or from disease of the muscle or neuromuscular junction. For example, isolated inferior rectus paresis may develop with trauma, myasthenia gravis, or vascular disease and may also occur on a congenital or idiopathic basis (von Noorden, 1991). Lesions of the inferior rectus subnucleus, however, may also give rise to isolated weakness of the inferior rectus muscle (Chou, 1998; Lee, 2000b; Tezer, 2000). Isolated inferior rectus paresis may also occur on a supranuclear basis with a lesion selectively interrupting fibers descending from the right medial longitudinal fasciculus (MLF) to the inferior rectus subnucleus (Tezer, 2000). The levator palpebrae superioris muscles, the superior recti, and the constrictors of the pupils are affected bilaterally with nuclear lesions. Because medial rectus neurons probably lie at three different locations within the oculomotor nucleus, it is unlikely that a medial rectus paralysis (unilateral or bilateral) would be the sole manifestation of a nuclear lesion (Umapathi, 2000). Most characteri-
Lesions affecting the third nerve nucleus
- Oculomotor nucleus: ipsilateral complete cranial nerve (CN) III palsy; contralateral ptosis and superior rectus paresis
- Oculomotor subnucleus: isolated muscle palsy (e.g., inferior rectus)
- Isolated levator subnucleus: isolated bilateral ptosis

Lesions affecting the third nerve fasciculus
- Isolated fascicle: partial or complete isolated CN III palsy with or without pupil involvement
- Paramedian mesencephalon: plus-minus syndrome (ipsilateral ptosis and contralateral eyelid retraction)
- Fascicle, red nucleus/cerebellar peduncle: ipsilateral CN III palsy with contralateral ataxia and tremor (Claude)
- Fascicle and cerebral peduncle: ipsilateral CN III palsy with contralateral hemiparesis (Weber)
- Fascicle and red nucleus/substantia nigra: ipsilateral CN III palsy with contralateral choreiform movements (Benedikt)

Lesions affecting the third nerve in the subarachnoid space
- Oculomotor nerve: complete CN III palsy with or without other cranial nerve involvement; superior or inferior division palsy

Lesions affecting the third nerve in the cavernous sinus
- Cavernous sinus lesion: painful or painless CN III palsy; with or without palsies of CN IV, VI, and V1; CN III palsy with small pupil (Horner syndrome); primary aberrant CN III regeneration

Lesions affecting the third nerve in the superior orbital fissure
- Superior orbital fissure lesion: CN III palsy with or without palsies of CN IV, VI, and V1; often with proptosis

Lesion affecting the third nerve in the orbit
- Oculomotor nerve: CN III palsy; superior or inferior CN III branch palsy
- CN III and optic nerve or other orbital structures: visual loss; proptosis; swelling of lids; chemosis

**Table 11-2. The Localization of TNP (Structure Involved: Clinical Manifestation)**

<table>
<thead>
<tr>
<th>Lesions affecting the third nerve nucleus</th>
<th>Lesions affecting the third nerve fasciculus</th>
<th>Lesions affecting the third nerve in the subarachnoid space</th>
<th>Lesions affecting the third nerve in the cavernous sinus</th>
<th>Lesions affecting the third nerve in the superior orbital fissure</th>
<th>Lesion affecting the third nerve in the orbit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oculomotor nucleus: ipsilateral complete cranial nerve (CN) III palsy; contralateral ptosis and superior rectus paresis</td>
<td>Isolated fascicle: partial or complete isolated CN III palsy with or without pupil involvement</td>
<td>Oculomotor nerve: complete CN III palsy with or without other cranial nerve involvement; superior or inferior division palsy</td>
<td>Cavernous sinus lesion: painful or painless CN III palsy; with or without palsies of CN IV, VI, and V1; CN III palsy with small pupil (Horner syndrome); primary aberrant CN III regeneration</td>
<td>Superior orbital fissure lesion: CN III palsy with or without palsies of CN IV, VI, and V1; often with proptosis</td>
<td>Oculomotor nerve: CN III palsy; superior or inferior CN III branch palsy</td>
</tr>
<tr>
<td>Oculomotor subnucleus: isolated muscle palsy (e.g., inferior rectus)</td>
<td>Paramedian mesencephalon: plus-minus syndrome (ipsilateral ptosis and contralateral eyelid retraction)</td>
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<td></td>
<td></td>
<td>CN III and optic nerve or other orbital structures: visual loss; proptosis; swelling of lids; chemosis</td>
</tr>
<tr>
<td>Isolated levator subnucleus: isolated bilateral ptosis</td>
<td>Fascicle, red nucleus/cerebellar peduncle: ipsilateral CN III palsy with contralateral ataxia and tremor (Claude)</td>
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<tr>
<td></td>
<td>Fascicle and cerebral peduncle: ipsilateral CN III palsy with contralateral hemiparesis (Weber)</td>
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<tr>
<td></td>
<td>Fascicle and red nucleus/substantia nigra: ipsilateral CN III palsy with contralateral choreiform movements (Benedikt)</td>
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</table>

**Source:** Modified from Brazis, 2001, with permission from Lippincott Williams & Wilkins.

A characteristic of oculomotor nuclear involvement is unilateral TNP, weakness of the ipsilateral and contralateral superior rectus, and bilateral incomplete ptosis (Pratt, 1995). On rare occasions the ipsilateral superior rectus is spared while the contralateral superior rectus is paretic. Bilateral TNPs with sparing of the lid levators may also be caused by nuclear lesions (the central caudal levator subnucleus is spared) (Bryan, 1992). Isolated bilateral ptosis with sparing of the extraocular muscles and pupils may occur with lesions involving the levator subnucleus and sparing more rostral oculomotor subnuclei (Martin, 1996). After surgery for a fourth ventricle ependymoma, bilateral nuclear oculomotor palsies affecting only the levator and superior recti subnuclei have been described, resulting in third nerve paresis affecting only the levators and superior recti bilaterally (Sanli, 1995). Bilateral total ophthalmoplegia, bilateral complete ptosis, and large, unreactive pupils have been described with midbrain hematoma (Worthington, 1996). This constellation of findings was thought due to bilateral third nerve nuclear or fascicular damage or both, bilateral involvement of the interstitial nucleus of Cajal and the rostral nucleus of the MLF, and involvement of bilateral horizontal saccadic and smooth pursuit pathways.
<table>
<thead>
<tr>
<th>Topographical Localization</th>
<th>Etiologies</th>
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</thead>
<tbody>
<tr>
<td>Nuclear TNP</td>
<td>Infarction or hemorrhage (Bengel, 1994; Bogousslavsky, 1994; Bryan, 1992; Chee, 1990; Gaymard, 1990; Saeki, 2000a; Tezer, 2000; Worthington, 1996)</td>
</tr>
<tr>
<td>Tumor</td>
<td>(Chou, 1998; Nakao, 1998; Sanli, 1995)</td>
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<tr>
<td>Infection</td>
<td></td>
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<tr>
<td>Trauma</td>
<td></td>
</tr>
<tr>
<td>Multiple sclerosis</td>
<td>(Lee, 2000b)</td>
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<tr>
<td>Fascicular TNP</td>
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<tr>
<td>Tumor</td>
<td>(Andreo, 1994; Barbas, 1995; Eggenberger, 1993; Ishikawa, 1997; Landolfi, 1998; Vetrugno, 1997)</td>
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<tr>
<td>Multiple sclerosis</td>
<td>(Newman, 1990; Onozu, 1998; Thömke, 1997)</td>
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<tr>
<td>Stereotactic surgery</td>
<td>(Borras, 1997)</td>
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<tr>
<td>Subarachnoid space</td>
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<tr>
<td>Ectatic vessels (Hashimoto, 1998b; Nakagawa, 1991; Zingale, 1993)</td>
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<tr>
<td>Infectious or inflammatory processes of the meninges (e.g., sarcoidosis and Wegener’s) and carcinomatous or lymphomatous meningitis (Balm, 1996; Galetta, 1992; Guarino, 1995; Ing, 1992; Ishibashi, 1998; Jacobson, 2001; Keane, 1993; Mark, 1992; McFadzean, 1998; Newman, 1995; Renowden, 1993; Straube, 1993; Ueyama, 1997)</td>
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<tr>
<td>Ophthalmoplegic migraine (O’Hara, 2001)</td>
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<tr>
<td>Subarachnoid hemorrhage with leukemia (Papke, 1993)</td>
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<tr>
<td>Pseudotumor cerebi</td>
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<tr>
<td>Spontaneous intracranial hypotension (Ferrante, 1998)</td>
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<tr>
<td>Trauma, especially during neurosurgical procedures (Balcar, 1996; Hedges, 1993; Horikoshi, 1999; Kudo, 1990; Lepore, 1995)</td>
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<tr>
<td>Nerve infarction from diabetes, atherosclerosis, giant cell arteritis, or systemic lupus erythematosus (nerve infarction may also occur in the cavernous sinus or anywhere along the course of nerve) (Berlit, 1991; Bondenson, 1997; Capo, 1992; Cullom, 1995; Davies, 1994; Jacobson, 1994, 1995, 1998a, 2001; Naghmi, 1990; Renowden, 1993; Richards, 1992)</td>
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<tr>
<td>Uncal herniation</td>
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<tr>
<td>Hydrocephalus</td>
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<tr>
<td>Cavernous sinus/superior orbital fissure</td>
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<tr>
<td>Aneurysm of the internal carotid or posterior communicating artery (Hahn, 2000; Ikeda, 2001; Jacobson, 2001; Keane, 1996; Lanzino, 1993; Silva, 1999; Zingale, 1997)</td>
<td></td>
</tr>
</tbody>
</table>

(continued)
Table 11-3. (continued)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Reference(s)</th>
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<tbody>
<tr>
<td>Ballon test occlusion of the cervical internal carotid artery (Lopes, 1998)</td>
<td></td>
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<tr>
<td>Cavernous sinus thrombosis or infection (e.g., tuberculoma); superior ophthalmic vein thrombosis (Bikhazi, 1998; Grayeli, 1998; Holland, 1998; Polito, 1996)</td>
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<tr>
<td>Tumors, including pituitary adenoma, meningioma, esthesioneuroblastoma, arachnoid cyst, neurinoma, nasopharyngeal carcinoma, myeloma, lymphoma, Hodgkin’s disease, and metastases (Barr, 1999; Cullom, 1993; Ing, 1997; Kasner, 1996; Keane, 1996; Kurokawa, 1992; Lee, 2000c; Liu, 1993; Manabe, 2000; Moster, 1996; North, 1993; Shen, 1993; Tao, 1992; Wake, 1993)</td>
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<tr>
<td>Pituitary infarction or hemorrhage (pituitary apoplexy) (Lee, 2000c; Robinson, 1990; Rossitch, 1992; Seyer, 1992)</td>
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<td>Gammopathy</td>
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<td>Intraneural hemorrhage (Miyao, 1993)</td>
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<td>Mucocele of the sphenoid sinus (Ashwin, 2001)</td>
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<tr>
<td>Sphenoid sinusitis (Chotmongkol, 1999)</td>
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<tr>
<td>Tolosa-Hunt syndrome, Wegener’s granulomatosis, or other granulomatous diseases (Herman, 1999; Jacobson, 2001; Keane, 1996)</td>
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<td>Orbit</td>
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<td>Infections, inflammations, and granulomatous processes (e.g., orbital pseudotumor) (Kondoh, 1998; Ohtsuka, 1997; Stefanis, 1993)</td>
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<tr>
<td>Sphenoid sinus mucocele (Sethi, 1997)</td>
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<td>Tumors (Goldberg, 1990a,b)</td>
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<td>Dural arteriovenous malformation (Gray, 1999)</td>
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<tr>
<td>Trauma</td>
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<tr>
<td>Unknown localization</td>
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<td>Congenital (Good, 1991; Hamed, 1991; Ing, 1992; Mudgil, 1999; Parmeggiani 1992; Patel, 1993; Pratt, 1995; Schumacher-Feero, 1999; Tsaloumas, 1997; White, 1992)</td>
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<tr>
<td>Migraine (Mark, 1998; O’Halloran, 1999; Prats, 1999)</td>
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<td>Viral infections (including herpes zoster ophthalmicus or Ramsay Hunt syndrome) and immunizations (Capoferri, 1997; Chang-Godinch, 1997; Mansour, 1997; Saeki, 2000c; Sood, 1999; Zurevinsky, 1993)</td>
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<td>Lyme disease (Savas, 1997)</td>
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<td>Diffuse neuropathic processes (e.g., Fisher’s syndrome and chronic inflammatory polyradiculo-neuropathy (CIDP) (Arroyo, 1995; Nagaoka, 1996)</td>
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<tr>
<td>Cervical carotid artery dissection, stenosis, or occlusion (Balcar, 1997; Hollinger, 1999; Koennecke, 1998; Mokri, 1996; Schievink, 1993)</td>
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<td>Subdural hematomas (Okuchi, 1999; Phookan, 1994)</td>
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<td>Glioblastoma multiforme (Al-Yamany, 1999)</td>
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<td>Unintentional subdural catheter (Haughton, 1999)</td>
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<td>Submucosal diathermy to the inferior turbinate to improve the nasal airway (Green, 2000)</td>
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<td>Toxic effects of drugs (Pacifici, 1993; Soysal, 1993)</td>
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<td>Cocaine (Migita, 1998)</td>
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<td>Sildenafil citrate (Viagra) (Donahue, 1998)</td>
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<tr>
<td>Internal carotid cisplatin infusion (inferolateral trunk carotid artery neurovascular toxicity) (Alderson, 1996; Wu, 1997)</td>
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<td>Dental anesthesia</td>
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<tr>
<td>Radiation therapy (Ebner, 1995)</td>
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<tr>
<td>Partial TNP associated with elevated anti-galactocerebroside and anti-GM 1 antibodies (Go, 2000)</td>
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</table>
Is the TNP Due to a Fascicular Lesion?

Lesions of the third nerve fascicle often accompany nuclear lesions because infarction is a common cause of a nuclear TNP, and the paramedian branches near the top of the basilar artery often feed both structures. For example, infarction of the dorsal paramedian midbrain may cause bilateral ptosis associated with unilateral paresis of all other muscles innervated by the oculomotor nerve (pupil spared) with sparing of the contralateral superior rectus muscle (Liu, 1991). These unique findings suggest a lesion of the proximal third nerve fascicles and the central caudal subnucleus. Third nerve fascicular lesions are often caused by infarction, hemorrhage, or demyelination. Pure fascicular lesions cause a unilateral peripheral type of oculomotor palsy. Involvement of brainstem structures other than the fascicle of the third nerve identifies the mesencephalic location of the lesion (Liu, 1992). Concomitant damage of the red nucleus and superior cerebellar peduncle causes contralateral ataxia and outflow tract cerebellar tremor (Claude’s syndrome), whereas a more anterior lesion, affecting the peduncle, gives rise to oculomotor palsy with contralateral hemiparesis (Weber’s syndrome). The TNP with Weber’s syndrome may affect or spare the pupillary fibers (Saeki, 1996).

Larger lesions that affect the oculomotor fascicle and the red nucleus/substantia nigra region may produce TNP with contralateral choreiform movements or tremor (Benedikt’s syndrome) (Borras, 1997), sometimes associated with contralateral hemiparesis if the cerebral peduncle is also involved. A pupil-sparing TNP associated with binocular ocular torsion to the contralateral side—thereby indicating a left-sided midbrain lesion that included the fascicle of the third nerve and the supranuclear integration centers for torsional eye movements, the interstitial nucleus of Cajal, and the rostral interstitial nucleus of the MLF—has been described with a paramedian rostral midbrain infarction in a diabetic with giant cell arteritis (Dichgans, 1995). Ipsilateral TNP and contralateral downbeat nystagmus may be caused by unilateral paramedian thalamopeduncular infarction (Oishi, 1997).

Rarely, a unilateral or bilateral fascicular third nerve lesion may occur in isolation without other ocular motor or neurologic signs or symptoms (see below) (Andreo, 1994; Barbas, 1995; Getenet, 1994; Kim, 1993; Newman, 1990; Thömke, 1995). Fascicular lesions, even when bilateral, may occasionally spare the pupil(s). Bilateral preganglionic internal ophthalmoplegia has been described with bilateral partial oculomotor fascicular lesions (Hashimoto, 1998a). Because of the intraaxial topographic arrangement of fibers, fascicular lesions may cause TNP limited to specific oculomotor-innervated muscles (Ksiazek, 1994). Fascicular lesions have resulted in the following:

1. Isolated inferior oblique paresis (Castro, 1990)
2. Unilateral fixed, dilated pupil unassociated with other neurologic dysfunction (Shuaib, 1989)
3. Paresis of the superior rectus and inferior oblique without other evidence of oculomotor nerve involvement (Gauntt, 1995)
4. Paresis of the superior and medial rectus (Saeki, 2000a)
5. Paresis of the levator muscle, superior rectus, and medial rectus (Onozu, 1998)
6. Paresis of the inferior oblique, superior rectus, medial rectus, and levator muscle with sparing of the inferior rectus muscle and pupil (Naudea, 1983; Schwartz, 1995; Shuaib, 1987)
7. Paresis of the inferior oblique, superior rectus, medial rectus, levator, and inferior rectus with pupillary sparing (Breen, 1991; Naudea, 1983)
8. Paresis of the left inferior rectus, left pupil, right superior rectus, convergence, and left medial rectus (Umapathi, 2000).

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 (Castro, 1990). 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 (Saeki, 2000a; Schwartz, 1995). This model also accounts for the description of superior and inferior division oculomotor palsies. The superior division paresis involves the superior rectus and levator muscles without involvement of other groups (Guy, 1989a; Hriso, 1990; Ksiazek, 1989). 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 (Abdollah, 1990; Eggenberger, 1993; Ksiazek, 1989). Both divisional palsies may be associated with intraaxial midbrain lesions. Thus, although superior and inferior divisional TNP have classically been localized to anterior cavernous sinus or posterior orbital lesions, a divisional TNP may occur from damage at any location along the course of the oculomotor nerve, from the fascicle to the orbit (Ksiazek, 1989).

Fascicular TNP may occasionally be associated with ipsilateral ptosis and contralateral eyelid retraction (plus-minus lid syndrome) (Gaymard, 1992; Vetrugno, 1997). This syndrome occurs with a small lesion located in the paramedian mesencephalon. There is involvement of the ipsilateral levator palpebrae fascicles as they emerge from the central caudal nucleus (the central caudal nucleus is spared), and the inhibitory pathways projecting on the levator palpebrae motor neurons immediately before their entrance in the central caudal nucleus. The plus-minus syndrome has been described with bilateral glioma extending to the paramedian midbrain and thalamomesencephalic infarction; it also may occur with peripheral processes such as peripheral TNP, myasthenia gravis, orbital myositis, congenital ptosis, or orbital trauma.

Is the TNP Due to a Subarachnoid Lesion?

An isolated pupil spared peripheral TNP is most often related to an ischemic neuropathy or a lesion affecting its subarachnoid portion. Subarachnoid lesions may distort or injure the brainstem, and diffuse processes will show signs of meningeal irritation. Etiologies of TNP due to a subarachnoid lesion are outlined in Table 11–3. Third nerve schwannoma may cause a painful relapsing-remitting TNP mimicking the clinical syndrome of ophthalmoplegic migraine (Kawasaki, 1999). Monocular elevator paresis from isolated superior rectus and/or inferior oblique dysfunction may occur in neurofibromatosis type 2–related schwannoma (Egan, 2001). The third nerve is also susceptible to trauma in the subarachnoid space, especially during neurosurgical procedures (Hedges, 1993; Horikoshi, 1999; Kudo, 1990). Closed head trauma may cause TNP due to shearing injury resulting in distal fascicular damage or partial root avulsion (Balcar, 1996). Walter et al described two patients with TNP precipitated by minor head trauma with negative brain computed tomography (CT) scans who were subsequently discovered to have ipsilateral posterior communicating artery aneurysms.
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; or (2) the lesion compresses only the inferior portion of the nerve and spares the dorsally situated pupillomotor fibers. The TNP 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. Ptosis has been described in isolation as the sole manifestation of third nerve compression by a posterior communicating artery aneurysm (Good, 1990). Rarely, aneurysmal TNP may even be transient and clear spontaneously (Greenspan, 1990).

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 (Lustbader, 1988). Conversely, an isolated pupillary paralysis without ptosis or ophthalmoparesis is rarely caused by an aneurysm or other subarachnoid lesion (Kaye-Wilson, 1994; Wilhelm, 1995). Koennecke and Seyfert reported a patient with a common carotid artery dissection from intraoperative trauma whose mydriasis preceded a complete TNP by 12 hours (Koennecke, 1998).

Is the TNP Due to a Cavernous Sinus Lesion?

Lesions of the third nerve in the cavernous sinus often also involve the other ocular motor 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 frontal-orbital pain experienced by patients with enlarging aneurysms could thus be caused by direct irritation of the third nerve (Lanzino, 1993). 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 (Silva, 1999) 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 mid-position fixed pupil or from aberrant regeneration (see below). Ikeda et al described a patient with a painful, “severe” TNP with normal pupils due to a cavernous sinus aneurysm (Ikeda, 2001). Lesions in the neighborhood of the posterior clinoid process may for some time affect only the third nerve as it pierces the dura (e.g., breast and prostatic carcinoma) (Cullom, 1993). Medial lesions in the cavernous sinus, such as a carotid artery aneurysm, may affect only the ocular motor nerves but spare the more laterally located ophthalmic branch of the trigeminal nerve, resulting in painless ophthalmoplegia. Lesions that begin laterally present with retro-orbital pain first, and only later does ophthalmoparesis supervene. Lesions located in the cavernous sinus causing TNP are outlined in Table 11–3. The clinical findings and etiologies for processes
located in the superior orbital fissure are similar to those of the cavernous sinus syndrome.

Is the TNP Due to an Orbital Lesion?

Lesions within the orbit that produce third nerve dysfunction usually produce other ocular motor dysfunction as well as optic neuropathy and proptosis (Goldberg, 1990a,b). Lesions may extend from the cavernous sinus to the orbital apex and vice versa so that a clear distinction between the two syndromes may be impossible. 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 sphenocavernous lesion (Stefanis, 1993). However, as we noted, 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 (Guy, 1985), 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 (Guy, 1989b). Superior branch palsy has also been described with basilar artery aneurysm, intracavernous carotid aneurysm, migraine, diabetes, lymphoma, sphenoidal abscess, sphenoid sinusitis, frontal sinus mucocele, viral illness, meningitis, and after craniotomy (Chotmongkol, 1992, 1999; Ehrenpries, 1995; Guy, 1989b; Manabe, 2000; O’Halloran, 1999; Saeki, 2000c; Silva, 1999; Stefanis, 1993). Even ophthalmoplegic migraine may cause recurrent paroxysmal superior division oculomotor palsy. Isolated superior division-like paresis may be mimicked by myasthenia gravis (Dehaene, 1995). Isolated inferior division involvement has occurred with trauma, mesencephalic infarction and tumor (Abdollah, 1990; Eggenberger, 1993; Ksiazek, 1989), basilar artery aneurysm (Kardon, 1991), parasellar tumors (e.g., meningioma, schwannoma) (Carlow, 1990), viral illness, orbital dural arteriovenous malformation (Gray, 1999), as part of a more generalized vasculitic or demyelinating neuropathy (Cunningham, 1994), and in association with elevated antagalactocerebroside and anti-GM1 antibodies (Go, 2000). Inferior division involvement with tumors may be pupil-sparing, perhaps because of insidious tumor growth sparing pressure-resistant pupillomotor fibers.

Partial or complete TNP 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.

What Is the Evaluation of Nonisolated TNP?

Nonisolated TNP should undergo neuroimaging, with attention to areas suggested topographically by the associated neurologic signs and symptoms. Appropriate investigations and neuroimaging studies are directed at the precise area of interest, and this area is determined by the associated localizing features with the TNP (Brazis, 1991; Lee, 1999). In general, MRI with and without gadolinium enhancement is the neuroimaging modality of choice for all these processes (Renowden, 1993). Contrast-enhanced CT
scanning with narrow (2-mm) collimation is reserved for those patients who cannot
tolerate MRI or in whom MRI is contraindicated (e.g., pacemaker, claustrophobia,
metallic clips in head, etc.) (Renowden, 1993; Teasdale, 1990). CT scanning is also the
appropriate first-choice neuroimaging study in patients being evaluated for acute head
trauma or acute vascular events (infarction or hemorrhage). If there are clinical signs of
a meningeal process, lumbar puncture should be performed. The evaluation of a patient
with TNP is summarized in Figure 11–1.

Is the TNP Due to Trauma?

Traumatic isolated TNP (type 2) should undergo CT scanning to search for associated
central nervous system damage (e.g., subdural or intracerebral hematoma) as indicated
by associated neurologic signs and symptoms (Balcar, 1996; Hedges, 1993; Kudo,
1990; Lepore, 1995; Phookan, 1994). TNP after mild head trauma have been observed
in association with otherwise asymptomatic lesions (e.g., cerebral aneurysm) (Park-
Matsumoto, 1997; Walter, 1994). Although uncommon, neuroimaging may be
warranted in patients with TNP after minimal or trivial trauma to exclude mass lesions
or cerebral aneurysms (class III–IV, level C).

Is the TNP Congenital?

Congenital isolated TNP (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, and
digital anomalies (Good, 1991; Hamed, 1991; Ing, 1992; Parmeggiani, 1992; Patel, 1993;
Pratt, 1995; Shumacher-Feero, 1999; White, 1992). 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 regene-
ration, and usually trace reactive or nonreactive to light. Rarely the pupil may be spared.
Amblyopia is common (Schumacher-Feero, 1999). Most cases are spontaneous, but
familial cases have been described. We recommend MRI in all patients with congenital
TNPs, mainly to search for associated structural abnormalities of the brain (class III–IV,
level C).

Is the Isolated TNP Acquired and
Nontraumatic?

Acquired, nontraumatic isolated TNP (type 4) may occur with lesions localized
anywhere along the course of the third nerve from the fascicle to the orbit (Renowden
1993). For clinical purposes, isolated TNP may be divided into three types (types
4A–4C) (Jacobson, 1999; Lee, 1999; Trobe 1985) (Table 11–1).
Figure 11–1. Evaluation of third nerve palsy (TNP).
Does the Patient Have an Acquired Isolated TNP with a Normal Pupillary Sphincter with Completely Palsied Extraocular Muscles (Type 4A TNP)?

TNP with a normal pupillary sphincter and completely palsied extraocular muscles is almost never due to an intracranial aneurysm. However, a single patient has been described in whom a painless, pupil-sparing, but otherwise complete TNP was the only sign of an aneurysm arising from the basilar artery (Lustbader 1988). A similar painful TNP palsy has been described with an aneurysm in the cavernous sinus (Ikeda, 2001), and pupillary sparing may rarely occur with pituitary adenoma. This type of TNP is most commonly caused by ischemia, especially associated with diabetes mellitus. In a retrospective review of 34 consecutive cases of isolated atraumatic TNP, diabetes mellitus was the most common etiology accounting for 46% of the cases (Renowden 1993). Ischemic TNP may also occur with giant cell arteritis (Berlit, 1991; Bondenson, 1997; Davies, 1994; Renowden, 1993; Richards, 1992) and systemic lupus erythematosus. Pupil-sparing TNP has also been reported with sildenafil citrate (Viagra) (Donahue, 1998) and cocaine use (Migita, 1998). Significant risk factors for ischemic oculomotor nerve palsies include diabetes, left ventricular hypertrophy, and elevated hematocrit (Jacobson, 1994). 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 TNPs (Bortolami, 1993).

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. However, the pupil may be involved in diabetic oculomotor palsies (Naghmi, 1990), and diabetes may even cause a superior branch palsy of the oculomotor nerve. Pupil sparing has been documented in 62 to 86% of TNPs due to ischemia (Jacobson, 1998a). In a prospective study of 26 consecutive patients with diabetes-associated TNP, internal ophthalmoplegia occurred in 10 patients (38%) (Jacobson, 1998a). The size of anisocoria was 1 mm or less in most patients. Only two patients had anisocoria greater than 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 TNP occurs more often than has previously been recognized (14 to 32% in other studies), although the degree of anisocoria in any one patient is usually 1 mm or less. When commenting on this study, Trobe stated, “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” (Trobe, 1998).

Postmortem examinations in three diabetic patients have demonstrated pathologic changes in the subarachnoid or cavernous sinus portion of the nerves. Ischemic TNP with pupillary sparing, however, has also been reported due to fascicular damage with mesencephalic infarcts documented on MRI (Breen, 1991; Dichgans, 1995; Hopf, 1990; Murakami, 1994; Thömke, 1995). Keane and Ahmadi, however, noted that most diabetic TNP are peripheral (Keane, 1998). In their MRI study of 49 diabetic patients with isolated, unilateral TNPs, only one was found to have a brainstem infarct. Of eight diabetics with midbrain infarcts and TNPs, seven had other central nervous system findings and five had bilateral TNPs.

In a prospective study of 16 patients with ischemic TNPs, 11 (69%) had progression of ophthalmoplegia with a median time between reported onset and peak severity of
ophthalmoplegia of 10 days (Jacobson, 1995). Almost all patients with an ischemic TNP will improve within 4 to 12 weeks of onset of symptoms (Capo, 1992).

Sanders et al retrospectively studied 55 patients with vasculopathic TNP (Sanders, 2001). Of these, 42 (76%) had normal pupillary function. Of these 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 and only three (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 TNPs of vasculopathic origin have a diffuse pattern of paresis, whereas in the literature pupil-sparing TNPs of aneurysmal origin usually have a focal pattern of paresis.

Adults who develop type 4A TNP do not need angiography (Jacobson, 1999; Miller, 1999). An MRI scan need not be performed initially, as the yield for detecting a compressive lesion is very low, especially if the TNP resolves over time (class III–IV, level C). Neuroimaging should be performed in patients with no vasculopathic risk factors or in patients who do not improve by 12 weeks of follow-up (class III–IV, level B). Patients with type 4A TNP should be observed for the first 24 to 48 hours 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 sedimentation rate determination (Bondenson, 1997; Davies 1994). Temporal artery biopsy should be performed if the sedimentation rate is elevated or other systemic symptoms are present (class III–IV, level C). Myasthenia gravis may rarely mimic this type of TNP, so an evaluation (e.g., Tensilon or Prostigmin test, antiacetylcholine antibodies, etc.) should be considered, primarily in patients with fluctuating or fatiguing ptosis or ophthalmoplegia (class III–IV, level C). If the complete, pupil-spared TNP improves following a period of observation, no neuroimaging is required (class III–IV, level C). Some authors recommend noninvasive vascular studies (MRI with MR or CT angiography) in all patients with TNP, regardless of whether or not they have diabetes or any other systemic vasculopathy, with the one exception being patients with an otherwise complete TNP (i.e., complete ptosis, no adduction, no depression, no elevation) but normally reactive, isocoric pupils (Miller, 1999).

Does the Patient Have an Acquired Isolated TNP with a Normal Pupillary Sphincter and Incomplete Palsied Extraocular Muscles (Type 4B TNP)?

Patients with an incomplete motor TNP with pupillary sparing require an MRI scan to rule out a mass lesion. If the MRI 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 MR angiography (MRA) or CT angiography may well reveal an aneurysm or other vascular malformation and may eventually take the place of arteriography (Jacobson, 1999; Kaufman, 1994; McFadzean, 1998; Tomsak, 1991; Weinberg, 1996); however, at this time, cerebral angiography is the "gold standard" for the diagnosis of cerebral aneurysms (Davis, 1996; Trobe, 1998). 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 TNP. Jacobson and Trobe addressed whether or not MRA was adequate for evaluating for aneurysms in patients with TNP (Jacobson, 1999). They noted that in 46 well-documented aneurysms of the posterior communicating artery causing TNP, the aneurysm diameters ranged from 3 to 17 mm (median 8 mm); 42 of these (91.3%) measured 5 mm or more, and four (8.7%) measured less than 5 mm (Teasdale, 1990). They then investigated how sensitive MRA is in detecting aneurysms and found that MRA detected 64 (97%) of 66 aneurysms 5 mm or greater in diameter but only 15 (53.6%) of 28 aneurysms less than 5 mm in diameter. The relationship between aneurysm size and risk of rupture was then assessed. Among the 115 aneurysms 5 mm or greater, 15 (13.0%) ruptured. None of the 40 aneurysms with a diameter of less than 5 mm ruptured. Combining these data, the authors estimated that properly performed MRA will overlook only 1.5% of aneurysms that cause TNP 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 TNP. 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 greater than 70, symptomatic atherosclerotic cardiovascular disease, significant cardiovascular or renal disease, Ehlers-Danlos syndrome). In patients with type 4B TNP (pupil-sparing incomplete TNP) (plus patient age greater than or equal to 40 years and vasculopathic factors present), these authors recommend MRI followed by MRA if MRI does not disclose a nonaneurysmal cause. Catheter angiography is recommended if (1) worsening of extracocular muscle or iris sphincter impairment continues beyond 14 days; (2) iris sphincter impairment progresses to anisocoria > 1 mm (Jacobson, 1998a); (3) no recovery of function occurs within 12 weeks; or (4) signs of aberrant regeneration develop (Jacobson, 1999) (class IV, level U).

Pupil involvement is not diagnostic of aneurysmal compression, and up to 38% of presumed ischemic TNPs involve the pupil (Jacobson, 1998a). Thus, a certain number of negative cerebral angiograms would be expected in the evaluation of pupil involved TNP. The 1 to 2% risk of catheter angiography, however, must be considered in the decision for angiography. MRI and MRA are especially warranted for superior division TNP. Myasthenia gravis may rarely mimic a superior division TNP, so a Tensilon test should be performed in these cases. If a patient with a partial TNP 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 (class IV, level C). In cases of presumed or suspected subarachnoid hemorrhage, CT may be the preferred initial imaging study followed by cerebral angiography.
Does the Patient Have an Isolated Acquired TNP with Subnormal Pupillary Sphincter Dysfunction and Partial or Complete Extraocular Muscle Palsies (Type 4C TNP)?

Patients with a “relative pupil-sparing” TNP should have MRI 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 MRI 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” TNP and none of the patients demonstrated aneurysms (Cullom, 1995). 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, however, was based on an inadequate patient sample (class IV, level U). Jacobson reported 24 patients with relative pupil-sparing TNP 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 (Jacobson, 2001). Also, others have reported internal carotid, posterior communicating, and basilar artery aneurysms in isolated TNP with relative pupillary sparing. Thus, cerebral angiography may still be warranted if MRI is negative (class IV, level C). Because 10 to 38% of patients with ischemic TNPs have pupillary dysfunction (Capo, 1992; Jacobson, 1998a), 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 TNP) plus patient age greater than or equal to 40 and vascular risk factors present, the authors recommended MRI followed by MRA if MRI does not show a nonaneurysmal cause (Jacobson, 1999). Catheter angiography may still be required in these patients (class IV, level U).

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 TNPs may occur not only with extraaxial ischemic lesions but also in intraaxial (midbrain) lesions, in a small proportion of subarachnoid compressive lesions, and in a high proportion of cavernous sinus compressive lesions (Naudea, 1983).

Complete external and internal TNPs 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 TNP”), Jacobson and Trobe recommend MRI followed by catheter angiography if MRI does not disclose a nonaneurysmal cause (Jacobson, 1999). A fully dilated and nonreactive pupil occurs in up to 71% of patients with aneurysmal compression and TNP. Aneurysms impair the pupil in 96% of TNP, and the remaining 4% in which the pupil is spared have only partial TNP.
What Neuroimaging Procedures Should Be Considered in a Patient with an Isolated TNP?

Lee et al reviewed the literature on MRI/MRA, CT and CT angiogram (CTA), and catheter angiography in the management of the isolated TNP, and proposed the following guidelines (Lee, 2002):

1. Isolated complete or partial internal dysfunction (pupil dilated) with completely normal external function of the third nerve and no ptosis: The risk for aneurysm in this setting is minimal and neuroimaging for aneurysm is probably not required. The papers that were reviewed in this manuscript, however, did not explicitly include or exclude isolated dilated pupils in their complete or incomplete TNPs. The clinician should look for other etiologies for isolated pupil dysfunction (e.g., tonic pupil, pharmacologic, sphincter damage). This represents a practice guideline of moderate certainty based on class III–IV evidence (level B).

2. Partial external dysfunction TNP without internal dysfunction: The risk for aneurysm in patients with partial TNP is moderate (up to 30% of cases). Unfortunately, the risk for an individual patient is not well defined because other etiologies may cause a partial external dysfunction TNP with a normal pupil. For example, patients who have clear myasthenia gravis do not require additional aneurysm evaluation. Other nonaneurysmal etiologies including neoplastic, demyelinating, infiltrative, and ischemic etiologies may also cause a partial TNP without pupil involvement and may require neuroimaging. If the TNP is due to aneurysm, the TNP usually progresses over time to a complete TNP including pupil involvement. Although there may not be internal dysfunction (pupil involvement) in a partial external dysfunction TNP, the term *pupil sparing* is probably not appropriate in this setting. That is, pupil involvement may occur over time in patients with partial TNP due to aneurysm with initially no internal dysfunction. Absence of pupil involvement early in the course of a partial TNP may be due to incomplete compression of the pupil fibers by the aneurysm.

MRI with MRA or CTA in the acute setting is a reasonable screen in these cases. The patient should be followed clinically for progression or pupil involvement in the first week. If the cranial MRI with MRA or CTA is negative and if the risk of angiography (e.g., elderly, severe cardiovascular disease, abnormal serum creatinine) is high, then observation alone is reasonable and the clinician should look for alternative etiologies for a partial external dysfunction TNP (e.g., myasthenia gravis). The clinician should still consider catheter angiography in these cases if the risk of aneurysm is higher than the risk of angiography (technically inadequate MRA, progression to complete TNP, pupil involvement). The practice option for cranial MRI with MRA or CTA alone in this setting is of low certainty (level C) and is based on class III–IV evidence.

3. Complete external dysfunction with completely normal internal function TNP: This clinical situation indicates a very low risk for aneurysm, and the vasculopathic patient may be observed for improvement. The pupil should be reexamined within the first week. Patients who develop pupil involvement should be evaluated using the recommendations outlined in the pupil-involving TNP sections of this chapter. If the patient has no vasculopathic risk factors, or if there is no improvement after 4 to 12 weeks, or if signs of aberrant regeneration develop, then cranial MRI with MRA or
CTA should be performed. This practice guideline is of moderate certainty based on the available evidence (level B). Evaluation for myasthenia gravis should be considered in painless, nonproptotic, pupil-spared ophthalmoplegia depending on the clinical situation.

4. Partial external dysfunction with partial internal dysfunction TNP: An initial cranial MRI with MRA (or CTA) is reasonable. If these studies are of excellent quality and negative, then the clinician should follow the patient for progression or complete internal dysfunction. The risk for aneurysm in this setting, however (even with a negative MRI/MRA), is uncertain. Clinicians should still consider catheter angiography if the risk of aneurysm in an individual patient is higher than the risk of angiography. This practice option is of low to moderate certainty in patients with low clinical risk for aneurysm based on class III–IV evidence (level C), and there is some disagreement among experts (level U).

5. Complete external dysfunction with partial internal dysfunction TNP: The risk of aneurysm for complete external dysfunction with partial internal dysfunction (partial pupil or “relative pupil sparing”) is also unknown but probably lower than that for partial external dysfunction with or without partial internal dysfunction. The risk for aneurysm in this setting (even with a negative MRI/MRA or CTA) is uncertain. The clinician should consider catheter angiography if the risk of aneurysm is deemed higher than risk of angiography. This practice option is of low to moderate certainty in patients with low clinical risk for aneurysm based on class III–IV evidence (level C), and there is significant disagreement among experts (level U).

6. Isolated complete internal dysfunction with partial or complete external dysfunction TNP: This clinical situation has the highest risk for aneurysm (86 to 100% of aneurysmal TNP’s have pupil involvement). MRI with MRA or CTA of the head should be performed, but even with negative neuroimaging there should be a strong consideration for catheter angiography. This practice guideline is of moderate certainty based on class III evidence and consensus expert opinion (level B). There are insufficient data to make a recommendation on whether a catheter angiogram must be performed in these cases (level U).

7. Any patient with TNP and signs of subarachnoid hemorrhage (SAH): The presence of SAH (on unenhanced CT scan or lumbar puncture [LP]) essentially makes the issue of complete or incomplete TNP as well as application of the “rule of the pupil” moot. Unfortunately, most of the papers in the literature on aneurysm and TNP have included nonneurologically isolated cases including SAH. In general, an initial CT scan (with consideration for an LP) should be performed in patients with TNP and signs of SAH. The clinical picture of SAH (e.g., severe headache, meningismus, altered consciousness) can be mimicked by other intracranial etiologies such as pituitary apoplexy, and most clinicians would consider a CT scan as an initial neuroimaging study prior to consideration of angiography. Patients with SAH on CT scan should probably undergo catheter angiography. Patients who cannot undergo a catheter angiogram (e.g., morbidly obese and unable to be placed on the angiography table) may have to undergo cranial CT and CTA alone prior to intervention. In other cases of SAH, special MRI parameters including fluid attenuation inversion recovery (FLAIR) MRI and MRA may be useful. Catheter angiography should be strongly considered even if the evaluations for SAH (e.g., CT, LP) are negative. This practice guideline is of strong certainty based on class II–III evidence and consensus expert opinion (level B).
8. Patients who cannot undergo MRI or MRA: CT and CTA could be considered in selected cases especially if MRA is not available or in cases where MRI is contraindicated (e.g., obesity, claustrophobia, pacemaker). Although CTA has some advantages over MRA (especially if the location of the aneurysm is known), the superior quality of MRI compared to CT in evaluating the entire course of the third nerve makes the combination of MRI/MRA superior to CT/CTA as the screening study for TNP. There is insufficient evidence to determine if a combination of MRI and CTA would be superior to MRI/MRA in patients with TNP. At the time of this writing, the use of CT/CTA would be considered a practice option in the evaluation of TNP, and the recommendation is of low certainty based on limited class III evidence (level C).

Is the TNP Progressive or Unresolved (Type 5 TNP)?

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

Is the TNP Associated with Signs of Aberrant Regeneration (Type 6)?

Months to years after the occurrence of a TNP, 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 optokinetonic 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. Lagophthalmos, presumably caused by co-contraction of the levator and superior rectus muscles during Bell’s phenomenon, has also been described (Custer, 2000).

Aberrant regeneration may be seen after TNP due to congenital causes, trauma, aneurysm, migraine, and syphilis, but is very rarely, if ever, caused by ischemic neuropathy (Barr, 2000; Custer, 2000). A single case of aberrant regeneration has been described after an ischemic stroke affecting the third nerve fascicle in the cerebral peduncle (Messe, 2001). 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 (Lee, 1992). 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 TNP (Landau, 1997). Primary aberrant regeneration may rarely occur with extracavernous lesions, such as neurilemmoma, meningioma, asymmetric mammillary body, or intradural aneurysm (Varma, 1994). Bilateral primary aberrant regeneration may also occur with abetalipoproteinemia (Bassen-Kornzweig syndrome) (Cohen, 1985). On rare occasions, the pseudo–von Graefe phenomenon may develop contralateral to a regenerating paretic third nerve (Guy, 1989b).

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

Retrospective Review of TNP

A previous retrospective study reviewed all patients with the diagnosis of TNP at a single tertiary care referral center (Baylor College of Medicine) from May 1992 to May 1996 (Lee, 1999). Ninety-one patient records were reviewed. A complete (i.e., involvement of all the somatic branches of the third cranial nerve) TNP was present in 79 cases (87%) and a partial TNP was present in 12 cases (13%). The pupil was completely uninvolved (i.e., pupil-spared) in 49 cases (54%), involved to some degree in 40 cases (44%), and inadequately documented in two cases (2%). The etiology of the TNP was presumed to be vasculopathic or ischemic in 16 cases (18%), intracranial tumor in 15 cases (16%), trauma in 14 cases (15%), congenital in nine cases (10%), aneurysm in eight cases (9%), postsurgical or iatrogenic in eight cases (9%), cerebrovascular accident in seven cases (8%), and miscellaneous or idiopathic in 14 cases (15%).

Of the 91 cases, the TNP was not isolated in 38 (42%) and isolated in 53 cases (58%). Of the 38 nonisolated TNP (type 1), 35 (92%) underwent neuroimaging. Two of the patients who were not imaged were referred for strabismus surgery for congenital TNP. They were presumably imaged elsewhere, although this was not documented in the record. The other patient went directly to angiogram and was diagnosed with an angiogram. Two of these 38 patients had CT scans that would not have been performed if the imaging guide had been strictly followed, as neither patient had signs of subarachnoid hemorrhage or trauma, and both subsequently underwent appropriate MRI. No additional information was afforded by the CT scans.

Of the 53 cases of isolated TNP, 23 were over the age of 55 years; eight of these 23 (35%) underwent erythrocyte sedimentation rate testing, which was normal. None of the patients in our series were diagnosed with giant cell arteritis. Thirty-two cases had isolated, pupil-sparing ophthalmoplegia, and six of these patients underwent testing with edrophonium chloride (Tensilon), none of which were positive. One of the patients in our series was diagnosed with myasthenia gravis by acetylcholine receptor antibody testing. Thirty-two patients had isolated, pupil-spared TNP. Twenty-five of these cases were complete TNP (type 4A), and seven were partial (type 4B). Of the 32 patients, 15 cases had no known vasculopathic risk factors, and 17 cases (53%) had known vasculopathic risk factors. Of the 15 cases without a known vasculopathic risk factor, nine underwent neuroimaging. Five of these 15 cases were congenital TNP (type 3) and did not undergo neuroimaging. One patient was sent for strabismus surgery for an idiopathic TNP, and there was no documentation in the record of previous imaging.
studies. One patient in this group underwent a CT scan that would not have been performed according to the imaging guide for the reasons mentioned above. This CT scan did not reveal an etiology for the TNP; however, a subsequent MRI scan showed a cavernous sinus tumor. Of the isolated pupil-spared TNPs that were presumed to be vasculopathic in nature, all demonstrated improvement or resolution of the TNP over time and none of these patients developed any new neurologic disease. Of these 17 cases, 12 MRI scans and six CT scans were performed on these patients. Of the MRI scans, 10 would not have been performed according to the imaging guide. Six of these were vasculopathic, one patient had myasthenia gravis diagnosed by antiacetylcholine receptor antibodies, and one patient had trauma and had undergone CT scan, LP, and cerebral angiogram. Two MRI scans actually revealed small midbrain strokes; however, this did not affect treatment and both patients showed spontaneous recovery. Of the CT scans, four would not have been performed, three were performed in vasculopathic patients, and one CT scan disclosed a tumor that would have undergone an initial MRI scan according to the imaging guide.

Twenty-one patients had isolated pupil-involved TNP (type 4C). Of these 21 cases, all underwent neuroimaging and 13 of 21 had an identifiable intracranial etiology for the pupil-involved TNP. Eight patients required further studies, of which six underwent standard cerebral angiography and two underwent MR angiography. Three of these eight patients were found to harbor an intracranial aneurysm (posterior communicating artery). In this group, three MRI scans would not have been performed because each patient had signs of SAH and each underwent CT scan followed by angiogram. One CT scan would not have been performed because the patient had no signs of SAH and would have undergone an initial MRI scan rather than a CT scan.

In our series, patients with a nonisolated TNP thus had a significant chance of harboring an intracranial lesion. Sixty percent of 38 patients had intracranial pathology including tumor (48%), aneurysm (22%), stroke (16%), carotid cavernous fistula (4%), tuberculoma in the cavernous sinus (4%), and Tolosa-Hunt syndrome (4%).

References


