Cranial Nerve Palsies: What's New?

5

Anita A. Kohli, John Woo, Madhura A. Tamhankar, and Sahil Thakur

Anatomy

The IIIrd, IVth, and VIth cranial nerves innervate the extraocular muscles. The medial, inferior, superior recti and the inferior oblique muscles are supplied by the IIIrd nerve, the superior oblique by the IVth nerve, and the lateral rectus by the VIth nerve. The IIIrd nerve also innervates the levator palpebrae superioris and pupillary sphincter muscle. The extraocular muscles have abduction (lateral rectus), adduction (medial rectus), elevation (superior rectus), depression (inferior rectus), incyclotorsion (superior oblique), and excyclotorsion (inferior oblique) as their primary actions.

The third nerve nuclear complex is found in the midbrain, and is composed of one subnuclei (central caudal nucleus) for the levator palpebrae superioris and paired superior rectus subnuclei that supply the contralateral superior rectus [1, 2].

A. A. Kohli (✉)
Department of Ophthalmology and Visual Science, Yale University School of Medicine, New Haven, CT, USA

Department of Neurology, Yale University School of Medicine, New Haven, CT, USA

J. Woo
Department of Radiology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

M. A. Tamhankar
Department of Ophthalmology at the Scheie Eye Institute, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

Department of Neurology, Hospital of the University of Pennsylvania, Philadelphia, PA, USA

S. Thakur
Department of Ocular Epidemiology, Singapore Eye Research Institute, Singapore, Singapore

P. P. Chhablani (ed.), *Neuro-ophthalmic Disorders*, Current Practices in Ophthalmology, https://doi.org/10.1007/978-981-13-8522-3_5

The connections from the superior rectus subnuclei pass via the contralateral subnucleus, before joining the IIIrd nerve fascicle. In the event of a unilateral lesion, it causes bilateral superior rectus palsies which may be worse ipsilaterally. The preganglionic fibers from the VIth nerve nucleus in the pons connect to the third nerve nucleus in the brainstem, via the medial longitudinal fasciculus, which is a center for the conjugate horizontal movement of the eyes [3].

The IIIrd nerve fascicles then traverse the red nuclei, the cerebral peduncles, and exit the brainstem into the interpeduncular fossa. Subsequently, they enter the subarachnoid space and the cavernous sinuses, where they travel in the lateral walls, until separating into the superior and inferior divisions in the anterior cavernous sinus [4]. On reaching the orbit, the IIIrd nerve passes via the annulus of Zinn and on to the medial, inferior and superior recti and the inferior oblique. The preganglionic parasympathetic fibers travel along the inferior division of the third nerve from the cavernous sinus into the orbit, eventually synapsing in the ciliary ganglion before supplying the pupillary sphincter (miosis) and ciliary body (accommodation). The fibers run superficially along the third nerve, making them more susceptible to infiltration or compression.

The IVth nerve originates in the dorsal midbrain and has the longest intracranial course of all cranial nerves. It decussates immediately after exiting the brainstem, in the anterior medullary vellum so that each superior oblique muscle is innervated by the contralateral nerve nucleus. The trochlear nerve is thin (0.75–1 mm) and along its incisural course, it is hidden by the tentorium. The nerve then enters the cavernous sinus along the lateral wall, below the IIIrd nerve. It enters the orbit through the superior orbital fissure and runs medially to supply the superior oblique muscle.

The VIth nerve nuclei are located in the dorsal pons. The genu of the VIIth (facial) nerve lies immediately proximal to the VIth nerve nucleus. The VIth nerve fibers pass through the corticospinal tracts before exiting the brainstem ventrally, at the pontomedullary junction (Fig. 5.1). It travels over the clivus and under the petroclinoid ligament to enter the cavernous sinus. This is a narrow space and hence the nerve is susceptible to compression around this area. In the cavernous sinus, the nerve is inferolateral to the cavernous carotid artery, as it courses anteriorly. The postganglionic sympathetic fibers join the VIth nerve for a short course in the anterior cavernous sinus, prior to passing through, but don't synapse in the ciliary ganglion. On entering the orbit, the VIth nerve passes through the annulus of Zinn and supplies the lateral rectus muscle (Fig. 5.2).

Cranial Nerve Palsies

Congenital

While congenital absence or maldevelopment of any cranial nerve nuclei may occur and lead to ocular misalignment, recently the term congenital cranial dysinnervation disorders (CCDD) is being used to describe a wide variety of non-progressive

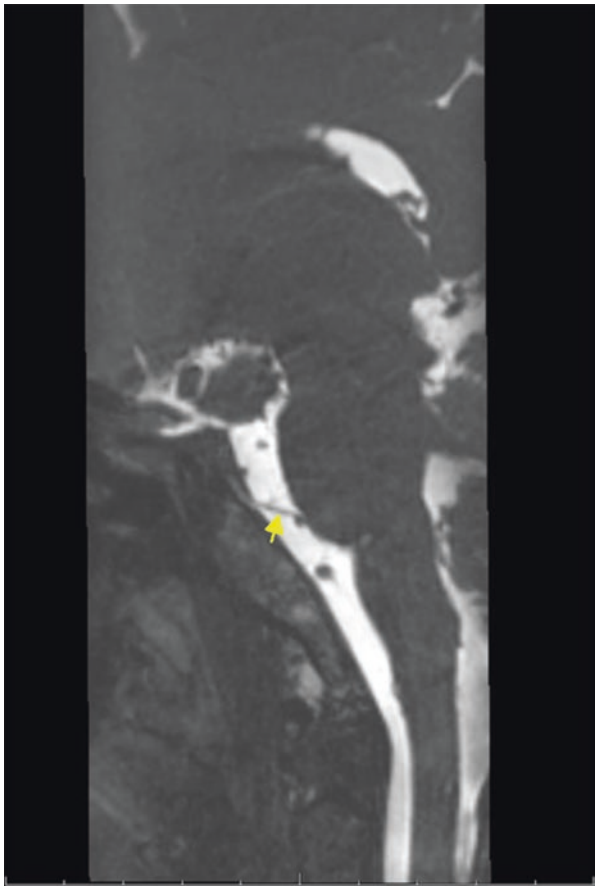

Fig. 5.1 3-T CISS MRI brain: oblique-sagittal view of pontomedullary junction. CISS (based on T2/T1 gradient) reconstruction demonstrating the ventral exit of the VIth nerve from the pontomedullary junction. Pathology involving the VIth nerve often occurs as the nerve courses over the bony clivus, after exiting from the midbrain

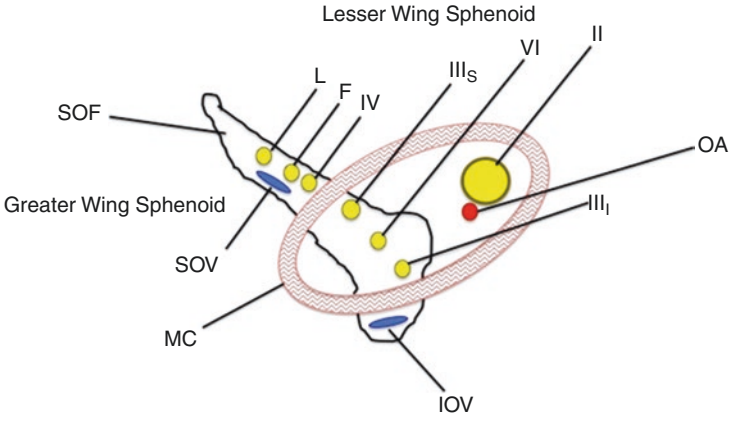

Fig. 5.2 The orbital apex, indicating the passage of the cranial nerves into the orbit. Note that the IVth cranial nerve is outside of the muscle cone (MC). *L* lacrimal nerve, *F* frontal nerve, *IV* cranial nerve IV, III_S superior division of cranial nerve III, *VI* cranial nerve VI, III_I inferior division of cranial nerve III, *II* cranial nerve II, *OA* ophthalmic artery, *IOV* inferior ophthalmic vein, *MC* muscle cone, *SOV* superior ophthalmic vein, *SOF* Superior orbital fissure

neurogenic syndromes. The most common CCDD is Duane syndrome, characterized by limitation of adduction, abduction, or both. Additionally, there is retropulsion of the globe and palpebral fissure narrowing on adduction. Huber classified Duane syndrome into three clinical subtypes: Type 1 is the most common and seen in 85% of the affected individuals and is characterized by limited abduction with or without esotropia, Type 2 with limited adduction with or without exotropia, and Type 3 in which both adduction and abduction are limited [5]. In most patients, there is absence or hypoplasia of the VIth nucleus or fascicle, and the lateral rectus is supplied by a branch of the IIIrd nerve [6, 7]. As opposing muscles are being supplied by the same nerve, co-contraction of both muscles during attempted abduction causes globe retraction and upshoots and downshoots due to tight horizontal recti muscles. Duane syndrome has been studied extensively and has confirmed genetic involvement of SALL4, HOXA1 (nerve development), and CHN1 (axonal guidance) genes. Neuroimaging studies have also showed that the primary cause is maldevelopment of the VIth nerve nucleus. Management of Duane syndrome involves spectacles for refractive correction, prisms for improvement in head position, amblyopia management, and surgical interventions for correction of deviation in primary position.

Moebius syndrome is another rare CCDD characterized by the presence of unilateral or bilateral VIIth nerve palsies along with VIth nerve palsy [8] most commonly, though the IIIrd and/or IVth nerves may also be involved. The syndrome is usually identified in infancy as infants have increased drooling or poor ability to suck [9]. Prenatal hypoxia to the developing fetus and drugs such as misoprostol, thalidomide, and cocaine have been reported to be associated with the syndrome [10, 11]. Genetic studies have shown malformations on chromosomes 1 and 13 with specific deletion of band 13q12.2. Neuroimaging usually demonstrates hypoplasia in the brainstem region around the pons where VIth and VIIth nerve nucleus are located. Congenital fibrosis of the extraocular muscles (CFEOM) is another rare disorder that is classified as CCDD. It is present at birth, is non-progressive, and runs in families. It causes varying degrees of ophthalmoplegia and ptosis. In most cases, the superior recti are dysfunctional, causing the eyes to be infraducted, with a compensatory chin up posture. Genetic studies have identified three types of CFEOM caused by mutations in KIF21A (CFEOM1), PHOX2A (CFEOM 2), and TUBB 3 gene (CFEOM3) [12, 13].

Brown syndrome was first described in 1950 and is thought to be caused by a short superior oblique tendon. Affected individuals exhibit limited elevation in adduction, near normal elevation in abduction, exotropia in upgaze and compensatory chin elevation to avoid diplopia [14].

Structural Intracranial Lesions and Brain Trauma

Structural intracranial lesions can often cause ocular motor palsies which may be isolated or accompanied by other neurological symptoms and signs. Evaluation of a patient presenting with ocular motor palsies is thus dependent on age, presence or

absence of other neurological signs and symptoms, prior history of brain trauma or surgery, and vasculopathic risk factors. Considering the high prevalence of vasculopathic comorbid conditions (diabetes and hypertension), cranial nerve palsies due to a vasculopathic etiology are a common diagnostic occurrence. These palsies typically resolve in 3–6 months from onset. However, in those patients who are <50 years of age or are relatively healthy, it is imperative to evaluate for other etiologies. Reports from case series indicate that in patients aged 21–50 with cranial nerve palsies, mass lesions were seen in 33%, with the majority located in the cavernous sinus [15]. Lee et al. studied the causes of VIth nerve palsies in the pediatric population and found that intracranial lesions or their subsequent surgical removal was the etiology in 45% of cases [16]. In a study of patients older than 50 years, Tamhankar et al. found that in 109 patients, vasculopathic risk factors were found in 61% of those who were identified with other etiologies for the ocular motor palsy, including midbrain infarcts, lymphoma, meningioma, and pituitary apoplexy. These authors also studied the need for early neuroimaging in isolated IIIrd, IVth, or VIth nerve palsies in older adults (>50 years) and reported that contrast-enhanced brain MRI is useful in the initial evaluation of these patients [17]. In a clinic, it is thus imperative to make decisions on a case-by-case basis. The presence of vasculopathic risk factors may point toward a more benign diagnosis, but neuroimaging is essential for a conclusive diagnosis. Additionally, tumors that inherent to the nerves themselves, such as schwannomas and neurinomas [18], should also be considered in the differential diagnosis and can be detected with high-resolution MRI (Fig. 5.3). In patients who have a history of brain trauma, and present with IIIrd nerve palsy, several points should be contemplated. Due to the long intracranial course of the IVth nerve, the proximity of the VIth nerve to the bony clivus, and the possibility of involvement of the IIIrd nerve from herniation or midline shift, involvement of

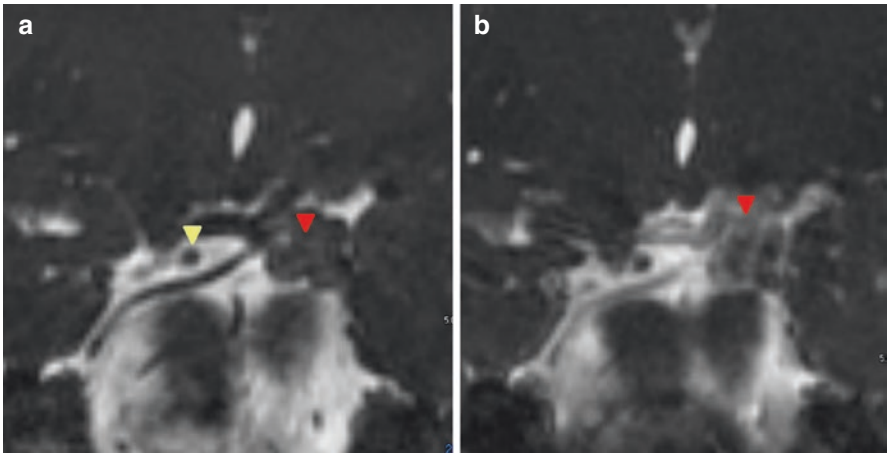

Fig. 5.3 3-T reformatted CISS MRI brain: coronal view of the midbrain demonstrating pre-contrast (**a**) and post-contrast (**b**) IIIrd nerve schwannoma with enhancement (red arrowhead). The yellow arrowhead (**a**) denotes normal IIIrd nerve

multiple cranial nerves is a common occurrence after head trauma. However, the magnitude and type of nerve involvement also depend on grade of head trauma. In a retrospective study of 210 patients with closed head injury, it was found that the severity of head injury was correlated with the type of cranial nerve palsies, such that patients with IIIrd nerve palsies had the highest incidence of severe head injury, those with IVth nerve palsies with an intermediate level of head injury, and those with VIth nerve palsies with the lowest level of head injury [19]. While spontaneous carotid artery dissections can occur rarely, many occur secondary to trauma. It is imperative to this etiology as a differential when the patient presents with diplopia, neck pain, head pain, and symptoms of retinal and cerebral ischemia. Patients with traumatic ocular motor palsies should be followed for at least 6–9 months, as they may have spontaneous resolution, negating the need for surgical intervention. Patching of one eye and prisms may be offered in the interim, but surgical intervention may be needed in those with intractable diplopia.

Inflammation or Infection

A wide variety of infectious and inflammatory etiologies can cause ocular nerve palsies in isolation or in combination with other neurological signs and symptoms. In the younger age group, demyelinating disease should be considered and is the second most common cause after mass lesions, though cranial nerve palsies are an uncommon presentation of demyelinating disease. In a study of 483 multiple sclerosis patients in 7.3%, a cranial nerve palsy was the presenting sign of the disease or of relapse in 3.1% [20]. Another case series found that multiple sclerosis caused 24% of non-traumatic VIth nerve palsies [16]. The patient prognosis in demyelinating disease depends on the early identification of the disease, so early neuroimaging should be considered in all younger patients presenting with ocular motor palsy.

Sarcoidosis is a systemic granulomatous disease that can cause CNS involvement in <5% of the affected patients [21]. The patient with isolated central nervous system sarcoidosis can present with intracranial mass lesions and multiple cranial nerve palsies. Histopathology is required for confirmation of typical epithelioid granulomatous inflammation in sarcoidosis. These lesions usually resolve with intravenous corticosteroids, and it is interesting to note that there may be no hilar adenopathy on chest imaging in these patients [22]. In another case report of undiagnosed neurosarcoidosis, Al-Qudah et al. presented a case of new onset seizure, left VIth nerve palsy, normal erythrocyte sedimentation rate, and MRI revealing dural thickening and enhancement of the left orbital apex. Dural biopsy confirmed sarcoidosis, and this patient also improved with high-dose IV corticosteroids, followed by an oral prednisone taper [23]. Neurosarcoidosis can also affect the IIIrd cranial nerve, as Bansal et al. presented a patient with an acute pupil involving IIIrd nerve palsy. Aneurysm was ruled out with computed tomographic angiogram, but MRI brain with contrast revealed enhancement of the IIIrd cranial nerve and leptomeningeal enhancement. Hilar lymph node biopsy was confirmatory of sarcoidosis, and this patient improved on IV steroids, prednisone taper, and methotrexate [24].

Diplopia is an uncommon presentation of giant cell arteritis (GCA), in the older population (>60 years), and occurs in 11.1% of the patients [25]. GCA is an important differential diagnosis, especially when patient presents with symptoms such as temple pain, jaw claudication, scalp tenderness, and unintentional weight loss. Vision loss may accompany or follow diplopia, and the diplopia can be transient. The diplopia is thought to be secondary to ischemia of the nerves supplying the extraocular muscles or the extraocular muscles themselves, along with ischemia of the cranial nerves [26]. In a prospective study by Tamhankar et al., three of the 109 patients studied with isolated ocular motor nerve palsy had GCA. All three had VIth nerve palsies and were diagnosed by positive temporal artery biopsies, after high ESR was detected during laboratory evaluations [18]. In another case series of IIIrd nerve palsy secondary to GCA, one of which had pupil involvement, two patients did not have systemic symptoms consistent with GCA, but had elevated serum inflammatory markers, and in another patient, inflammatory markers were normal, but the patient had systemic symptoms of GCA. All patients had the diagnosis confirmed with temporal artery biopsy and had resolution of the nerve palsy on high-dose oral prednisone [27]. This indicates that GCA can have a myriad variety of presentations; diagnosis, however, is confirmed on temporal artery biopsy and good steroid response. The initiation of prompt steroids for suspected GCA is thus a necessary part of the management of this disease. Liu and Chestnutt demonstrated that contrast-enhanced MRI of the orbits might be helpful in diagnosing GCA where immediate biopsy cannot be taken, as two cases presented with enhancement of the optic nerve sheath(s) in biopsy proven GCA [20]. Liu and Miller showed a case of unilateral anterior arteritic ischemic optic neuropathy with bilateral optic nerve sheath enhancement [21]. Therefore, in atypical presentations of giant cell arteritis, contrast-enhanced MRI may have a contributory role in formulating a working diagnosis. However, optic nerve sheath enhancement may be seen in several common inflammatory causes, such as sarcoidosis, optic neuritis, or nerve-related tumors, thus patient evaluation should be inclusive of these conditions. Patients may also complain of significant retrobulbar pain that may have a relapsing and remitting course.

Tolosa Hunt syndrome should also be considered if there is pain in combination with a IIIrd, IVth, VIth palsy or involvement of first division of the trigeminal nerve. The disease is characterized by inflammation that is exquisitely responsive to steroids, and some contend that its responsiveness to steroids can be used as a diagnostic criterion [28]. Neuroimaging should be undertaken to determine the extent of inflammation and to rule out other causes of painful ophthalmoplegia, such as infection via spread from the sphenoid sinus, especially before systemic steroids are prescribed.

Multiple cranial nerve palsies can also be associated with meningitis. Meningitis itself can be caused via many etiological factors. However, it appears that infectious meningitis by the herpesviridae family may be causative more often. While varicella zoster usually presents with a painful skin rash in the affected dermatome, the skin rash may not accompany cranial nerve palsies leading to diplopia, and the patient may not have encephalitis or meningitis, as shown by Yeh and Liao [29].

Human herpesvirus 6 can also cause cranial neuropathies, including one case of a IVth nerve palsy with concomitant acute retinal necrosis, in an immunocompetent patient [30]. Detection of the virus usually requires polymerase chain reaction of the cerebrospinal fluid or aqueous or vitreous humor. Though more common in children, petrous apicitis secondary to otitis media may lead to a VIth nerve palsy, as only a thin dura separates the VIth nerve and the trigeminal ganglion from the petrous apex. The triad of facial pain, VIth nerve palsy, and otitis media are found, it is termed Gradenigo syndrome [31]. Tuberculous meningitis also has a predilection for the skull base, causing cranial nerve palsies from dense bacterial exudates in the subarachnoid spaces [32]. Due to the involvement of this area, this has been used as a predictive factor to distinguish tuberculous meningitis from acute bacterial meningitis (OR: 1.980) [33]. Lyme disease may cause cranial neuropathy in the absence of Lyme meningitis, and therefore cranial nerve palsies may be seen with normal cerebrospinal fluid studies [34]. In children, Lyme meningitis may cause a pseudotumor cerebri-like syndrome that may lead to VIth nerve palsies [35].

Autoimmune

Myasthenia gravis (MG) is an autoimmune condition that may be localized to the eyes or become generalized to affect larger muscle groups. The disease is B-cell-mediated and is characterized by the presence of autoantibodies against the acetylcholine receptor or, less frequently, against muscle specific kinase (MUSK). Recently, autoantibodies against lipoprotein-related protein 4 (LRP4), titin, or ryanodine receptor have also been implicated [36]. Ocular involvement with myasthenia gravis causes diplopia, which can often mimic any ocular motor nerve palsy. The hallmark of this condition is fluctuating ocular misalignment with or without unilateral or bilateral ptosis. With widespread availability of testing autoantibodies against the acetylcholine receptor, it is desirable to obtain these in patients who complain of transient features of cranial nerve palsies. It has been shown that the binding and modulating antibodies are found with the same frequency in patients with MG, and the diagnostic yield is improved if both modulating and binding antibodies are assayed [37]. Binding and modulating antibodies are found in about 70% of those with ocular myasthenia [38]. Some patients may not be positive for these autoantibodies, even on repeated testing, and are referred to as seronegative. In seronegative patients in whom clinical suspicion for MG is high, single fiber electromyography of the orbicularis oculi muscle should be considered [39]. The first-line treatment for myasthenia gravis is pyridostigmine alone or in combination with other immunosuppressants, such as prednisone, azathioprine, mycophenolate mofetil, or rituximab in more refractory cases [40]. In absence or unavailability of single fiber electromyography, a therapeutic trial with pyridostigmine can be considered, and symptomatic improvement indicates MG. A chest CT should be performed to rule out thymoma, and thymectomy is indicated in patients who have suspected thymoma. Even in patients who do not have thymoma, thymectomy has been proven to be beneficial in patients <65 years old, with generalized myasthenia

gravis, as this may result in decreasing disease severity and less need for immunosuppression [41]. The effectiveness of thymectomy for ocular myasthenia gravis is unproven.

Miller Fisher syndrome is another rare disorder that presents with a triad of ophthalmoplegia, ataxia, and areflexia. The exact pathogenesis of this condition is unknown, although patients may report a preceding illness, and *Campylobacter jejuni* has been implicated in some cases [42]. Clinical features include demyelination of peripheral and central myelin sheaths, with elevated cerebrospinal fluid protein and presence of anti-GQ1B antibodies [43]. Management includes plasmapheresis, intravenous immunoglobulin, and supportive care.

Thyroid eye disease, which is an independent autoimmune process from primary thyroid disease, may mimic cranial nerve palsies due to fibrosis of extraocular muscles. The medial rectus is often involved, and this may mimic a VIth nerve palsy on examination [44]. Thyroid eye disease rarely cause actual cranial nerve palsies, unless there is significant extraocular muscle enlargement leading to orbital apex syndrome.

Evaluation of Patients with Ocular Motor Palsies

History

Patient history is the most important aspect in neuro-ophthalmic evaluation. Mostly patients with an ocular motor cranial nerve palsy complain of double or blurred vision that resolves on closing one eye. It is then important to consider whether diplopia was acute or of insidious onset, horizontal or vertical, worse in any direction of gaze or accompanied with other neurological signs or symptoms. The systemic history of the patient which includes history of vasculopathic risk factors, head trauma, prior ocular surgery, neurosurgery, tumors, or recent infections should be recorded. If the diplopia is binocular, the pattern of misalignment is helpful, as horizontal diplopia indicates the IIIrd or VIth nerve and vertical or oblique diplopia usually implies involvement of IIIrd or IVth nerves. History of strabismus, and prior interventions to manage strabismus should be discussed, as prior patching or surgery can account for a decompensated deviation. It is important to elicit and record history of prior episodes of diplopia, as this is an important clue to guide the neuro-ophthalmological evaluation.

Other associated clinical finding may strongly indicate a particular pathology like:

- New onset diplopia, difficulty swallowing, and ptosis: myasthenia gravis
- History of cardiovascular risk factors: vasculopathic factors
- History of multiple sclerosis and horizontal diplopia: internuclear ophthalmoplegia
- Focal neurological signs, such as confusion, imbalance, vertigo, and gait difficulties: intracranial lesions

The presentation of patient with a IIIrd nerve palsy is usually more subtle than the classical exodeviated and hypotropic eye with a blown pupil. The presentation usually

involves ipsilateral deficits in supraduction, infraduction, and adduction, with ptosis and a dilated, perhaps partially reactive, pupil. A lesion of the IIIrd nerve nucleus may cause bilateral ptosis and bilateral supraduction deficits, due to the paired levator subnucleus and the proximity of the superior recti subnuclei to one another. As the IIIrd nerve splits into the superior and inferior divisions in the anterior cavernous sinus, isolated superior division lesions may cause subtle ptosis and a supraduction deficit only. While it may be tempting to localize a divisional third nerve palsy to the cavernous sinus or orbital apex, it has been shown that divisional palsies may occur from a lesion anywhere along the length of the nerve, due to topographical organization of the nerve fibers prior to the anatomical bifurcation [45]. In a pupil sparing IIIrd nerve palsy, aneurysm and intracranial masses should also be considered, as the pupil may become involved later. Additionally, it is important to consider myasthenia gravis, as this condition may mimic a pupil sparing IIIrd nerve palsy.

Acute IVth nerve palsies are likely to occur after closed head trauma, and will cause vertical diplopia, worse in contralateral gaze and ipsilateral head tilt. In these patients, small degrees of vertical misalignment are quite visually debilitating. In those with >10° of excyclotorsion, measured by double Maddox rod, bilateral IVth nerve palsies should be considered. Congenital IVth nerve palsies occur in about one-third of patients, and examination of childhood pictures for facial asymmetry and head tilt is an important component of evaluation. Additionally, presence of inferior oblique overaction, lack of excyclotorsion, and large vertical fusional amplitudes all suggest a decompensated form of the deviation.

Patients with a VIth nerve palsy will have decreased abduction in that direction of gaze (left VIth nerve palsy leads to a deficit in abduction of the left eye). Occasionally, the extraocular movements will appear full, but there will be a small esodeviation when the eyes are abducted. Therefore, the presentation of a patient with VIth nerve palsy is horizontal binocular diplopia that worsens when looking toward the side of the lesion. Since this causes an esodeviation, the patient will likely be more symptomatic at distance. If there is ipsilateral facial weakness, a nuclear VIth nerve palsy should be suspected, due to the proximity of the VIth nerve nucleus and the genu of the facial nerve [46]. In patients without vasculopathic risk factors who develop a VIth nerve palsy that spontaneously resolves, skull base tumors should still be considered [47]. There is a report of two cases of a recurrent and spontaneously improving VIth nerve palsy in children secondary to skull base chondrosarcoma [48], which reiterates that all children with cranial nerve palsies must undergo neuroimaging. In patients with headaches and blurred vision, with or without optic disc edema, VIth nerve palsies from increased intracranial pressure may result. The differential diagnosis is extensive but includes pseudotumor cerebri, neoplasm, inflammation, infection, and mass lesions.

Examination

Patients require an ophthalmologic and focused neurological examination based on the presenting symptoms. Prior to beginning the examination, it is important to observe the patient's gait as they walk into the examination room and their facial

features for ocular misalignment, ptosis, facial asymmetry, and head position. Pupillary examination should be conducted in light and dark, as subtle differences can be indicative of pathologic states. Color vision is a sensitive indicator of optic nerve function, but familial dyschromatopsia, prior optic neuropathy or optic neuritis, and poor visual acuity may confound this measurement. Patients with shallow orbits may appear to have abduction deficits, but this should be accompanied by an esodeviation in that direction of gaze, if a true deficit exists. Versions and ductions (monocular testing) should be checked, with careful recording of deficits. There are many methods for the evaluation of ocular misalignment, including cover/uncover, alternate cover, Krimsky or Hirschberg techniques. Vertical misalignments can be measured using the Maddox rod in cooperative patients. As mentioned previously, the pattern of misalignment can used to uncover the pathology. However, long-standing deviations may have a spread of comitance, and the ocular misalignments are similar in all directions of gaze. A dilated eye examination should be undertaken on all new patients or known patients with new symptoms so as not to miss retinal or macular pathology.

Laboratory Tests

The laboratory tests are conducted to evaluate specific risk factors. In older patients, evaluation should include metabolic markers, such as hemoglobin A1C, comprehensive metabolic panel, and lipid levels. If GCA is a differential, assessment of the patient's inflammatory status should be undertaken immediately, and lab tests should include erythrocyte sedimentation rate and C-reactive protein. In patients suspected with myasthenia gravis, acetylcholine receptor antibody titers should be requested.

Imaging

Neuroimaging is indicated in patients who present with focal neurological signs, suspicion for multiple sclerosis, new onset headache, or have a complicated clinical picture. Contrast-enhanced MRI is modality of choice in such patients. Orbital imaging with thinner slices can be obtained, and evaluation of orbital structures or cavernous sinuses is required, which may be needed to differentiate actual cranial nerve palsies from mimickers, such as thyroid eye disease [44]. In the prospective study by Tamhankar et al. [18], 5% of patients had true intracranial pathologies, including giant cell arteritis, infarction, and neoplasm. This has been confirmed by other studies, suggesting an incidence of 1–14% of intracranial lesions accounting for cranial nerve palsies in older adults [49, 50]. While it may be argued that imaging one of every 100 patients to determine the prevalence of intracranial pathology [51] is not cost-effective, it has been shown that the actual cost of imaging, when compared to the clinically relevant findings uncovered, is reasonable [52]. It is also difficult to decide if neuroimaging is warranted depending on which cranial nerve palsy is present, as it has been thought that most IVth and VIth nerve palsies are due

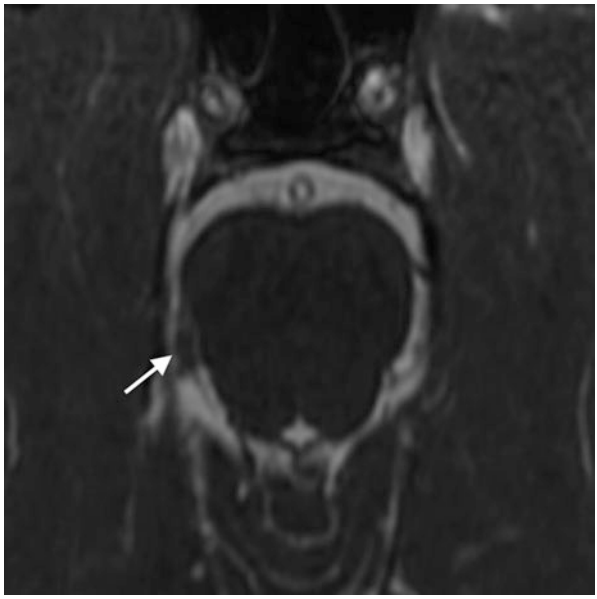

Fig. 5.4 1.5-T FIESTA-C sequence MRI brain: axial view of the midbrain. The fourth cranial nerve exits dorsally and travels through the ambient cistern ventrally. The arrow indicates a schwannoma of the right IVth nerve

to ischemia or demyelination and that neuroimaging may not alter patient management [51]. However, there have been reports of mass lesions causing isolated IVth nerve palsies (Fig. 5.4) [53]. Thus blanket statements suggesting that only certain cranial nerve palsies require neuroimaging should be interpreted with caution. The significantly higher occurrence of intracranial lesions causing cranial nerve palsies in children requires neuroimaging in all cases in this population.

With the advent of 3 Tesla (3 T) MRI scanners and special reconstruction sequences, the course of the cranial nerves can be followed intracranially, and may allow for more accurate localization and diagnosis. Kontzialis et al. found high-resolution 3D skull base MRI imaging for better image quality to image skull base area. In this protocol, 0.6-mm constructive interference in steady-state (CISS) images are obtained before and after gadolinium contrast infusion, based on T2/T1 signal, and the course of the VIth nerve, from brainstem to orbit, can be imaged (Figs. 5.5 and 5.6) [54]. Use of surface coils in a transparent face mask allows visualization of intraorbital motor nerves in a prospective study using high-resolution MRI [55]. The coils allow for 1–2-mm thick sections, and the FIESTA (fast imaging employing steady-state acquisition, analogous to CISS) sequence permits visualization of the cranial nerves against the cerebrospinal fluid background [56]. These images can also be obtained on a 1.5 Tesla scanner, so the additional use of surface coils allows older machines to also produce high-quality images. Similarly, Kau et al. used a similar technique to evaluate 12 patients with IIIrd nerve palsy. In two patients, who were previously stated to have normal MRI imaging, high-resolution MRI found enhancing tumors of the IIIrd nerve in the subarachnoid and intraorbital spaces, with associated atrophy of the extraocular muscles [57].

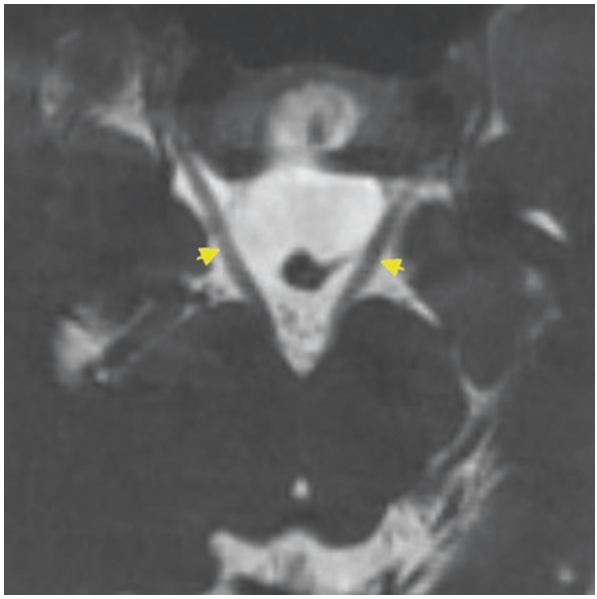

Fig. 5.5 3-T reformatted CISS MRI brain: oblique-axial view of midbrain demonstrating normal IIIrd nerves (arrows) exiting from the ventral midbrain

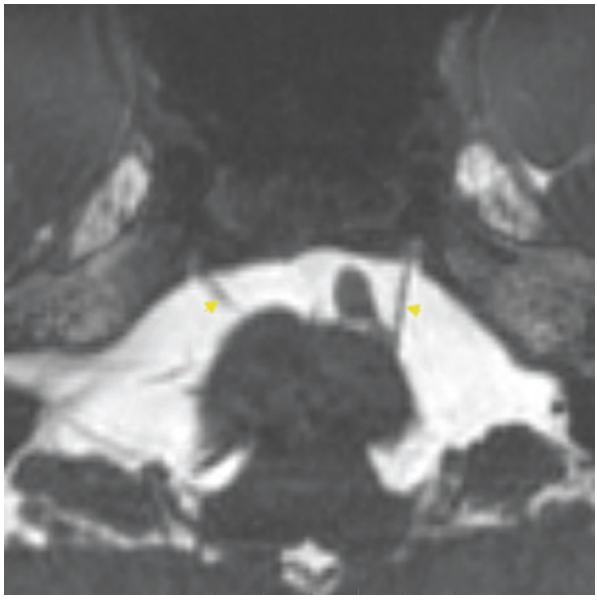

Fig. 5.6 3-T CISS MRI brain: oblique-axial view of pontomedullary junction showing normal VIth nerves (arrowheads) exiting the pontomedullary junction

Ultrahigh field MRI (7 Tesla) has also become available and offers imaging of small structures within and around the brainstem, such as the cranial nerves, with the spatial resolution approaching the sub-millimeter range [58]. When comparing 7 T to 3 T scanners (with head coil), cranial nerves III, V, and the VII/VIII complex can be imaged more readily, but due lack of availability, cost of use and longer scan times of 7 T MRI scanners are largely reserved for research use [59].

Cranial nerve trajectories can be tracked in three dimensions, via the identification of axonal direction using advanced diffusion MRI. Conventional diffusion tensor imaging (DTI) was a major step forward in imaging cranial nerves, but its use was limited by angular resolution, inability to resolve the origins of the cranial nerves, and significant artifact [60]. Newer methods such as high-definition fiber tractography (HDFT) have diminished these artifacts, and using this technology, HDFT can identify the cisternal portions of most cranial nerves in control patients [61]. Overall, these latest imaging techniques have the potential to increase the accuracy of diagnosis and localization of cranial nerve palsies. The cost of neuroimaging is, however, a factor that needs more attention in order to address limitation of availability in resource poor countries.

Treatment

Diplopia resulting from cranial nerve palsies may be managed with prisms or patching one eye. Usually a stick-on Fresnel prism is used initially to give the patient a sense of what prismatic correction will do for them, at the expense of reduced visual acuity. If they are comfortable, then ground-in prisms may be advised.

Fresnel prisms are useful in patients with debilitating double vision with a dynamic course of pathology, as they are inexpensive and easily replaceable. Contrary to the old belief that prismatic correction should not be considered for incomitant strabismus, careful prism selection can help, for example, patients with inferior incomitant vertical strabismus resulting from IVth nerve palsy. Prisms added in reading glasses can help alleviate diplopia in downgaze [62]. In a retrospective study of 64 patients with incomitant, large, and otherwise complex strabismus, it was found that 72% had complete or partial resolution of diplopia, and a larger majority of patients who prescribed vertical prisms reported improvement as compared to those who prescribed horizontal prisms [61]. Satisfaction with prismatic correction was also assessed based on etiology, and it was shown that 100% patients with divergence insufficiency and skew deviation reported improvement in diplopia in contrast to only 64% of those with convergence insufficiency [63]. In those with IVth nerve palsy, 80% of those treated with prism reported symptomatic relief, and a similar percentage reported satisfaction despite prescribing a >10 prism diopters prism [64]. Some patients are intolerant to prismatic correction. For such cases, patching one eye or prescribing fogged glasses provides symptomatic relief. If a patient has had stable strabismus examinations for many months, surgery can be considered. The surgical management of strabismus from cranial nerve palsies is beyond the scope of this chapter.

References

1. Warwick R. Representation of the extra-ocular muscles in the oculomotor nuclei of the monkey. J Comp Neurol. 1953;98:449–95.
2. Donzelli R, Marinkovic S, Brigante L, et al. The oculomotor nuclear complex in humans. Microanatomy and clinical significance. Surg Radiol Anat. 1998;20:7–12.

3. Fenichel G. Clinical pediatric neurology. 6th ed. Philadelphia: Elsevier; 2009. p. 313–31.
4. Bhatti M, Eisenschenk S, Roper S. Superior divisional third cranial nerve paresis, clinical and anatomical observations of 2 unique cases. Arch Neurol. 2006;63(5):771–6.
5. Traboulsi E. Congenital abnormalities of cranial nerve development: overview, molecular mechanisms, and further evidence of heterogeneity and complexity of syndromes with congenital limitation of eye movements. Trans Am Ophthalmol Soc. 2004;102:373–89.
6. Alexandrakis G, Saunders RA. Duane retraction syndrome. Ophthalmol Clin N Am. 2001;14(3):407–17.
7. Hotchkiss MG, Miller NR, Clark AW, Green WR. Bilateral Duane's retraction syndrome. A clinical-pathologic case report. Arch Ophthalmol. 1980;98(5):870–4.
8. Briegel W. Neuropsychiatric findings of Mobius sequence – a review. Clin Genet. 2006;70(2):91–7.
9. Kumar D. Moebius syndrome. J Med Genet. 1990;27:122–6.
10. Pastuszak AL, Schüler L, Speck-Martins CE, et al. Use of misoprostol during pregnancy and Möbius syndrome in infants. N Engl J Med. 1998;338:1881–5.
11. Puvabanditsin S, Garrow E, Augustin G, Titapiwatankaul R, Kuniyoshi KM. Polan-Mobius syndrome and cocaine abuse: a relook at vascular etiology. Pediatr Neurol. 2005;32(4):285–7.
12. Whitman M, Hunter D, Engle E. Congenital fibrosis of the extraocular muscles. Gene reviews. Seattle: University of Washington; 2016. p. 1993–2017.
13. Tischfield MA, et al. Human TUBB3 mutations perturb microtubule dynamics, kinesin interactions and axon guidance. Cell. 2010;140(1):74–87.
14. Parks M, Brown M. Superior oblique tendon sheath syndrome of brown. Am J Ophthalmol. 1970;7:82–6.
15. Peters G, et al. Cause and prognosis of nontraumatic sixth nerve palsies in young adults. Ophthalmology. 2002;109:1925–8.
16. Lee M, et al. Sixth nerve palsies in children. Pediatr Neurol. 1999;20:49–52.
17. Tamhankar M, et al. Isolated third, fourth and sixth cranial nerve palsies from presumed microvascular versus other causes, a prospective study. Ophthalmology. 2013;120:2264–9.
18. Celli P, Ferrante L, Acqui M, et al. Neurinoma of the third, fourth, and sixth cranial nerves: a survey and report of a new fourth nerve case. Surg Neurol. 1992;38:216–24.
19. Avinder D, West A, Trobe J, Musch D. Third, fourth, and sixth cranial nerve palsies following closed head injury. J Neuroophthalmol. 2006;26:4–10.
20. Zadro I, et al. Isolated cranial nerve palsies in multiple sclerosis. Clin Neurol Neurosurg. 2008;110:886–8.
21. Smith JK, Matheus MG, Castillo M. Imaging manifestations of neurosarcoidosis. AJR Am J Roentgenol. 2004;182:289–95.
22. Shimizu K, et al. Isolated neurosarcoidosis presenting with multiple cranial nerve palsies. Surg Neurol Int. 2016;7:44.
23. Al-Qudah Z, et al. Cranial nerve-VI palsy as the main clinical manifestation of neurosarcoidosis. Neurologist. 2016;21(6):109–11.
24. Bansal S, et al. Isolated pupil involving third nerve palsy as the first presentation of sarcoidosis. Neuro-Ophthalmology. 2014;38(5):278–80.
25. Hayreh SS, Podhajsky PA, Zimmerman B. Occult giant cell arteritis: ocular manifestations. Am J Ophthalmol. 1998;125(6):893.
26. Haering M, et al. Incidence and prognostic implications of diplopia in patients with giant cell arteritis. J Rheumatol. 2014;41:1562–4.
27. Thurtell M, Longmuir R. Third nerve palsy as the initial manifestation of giant cell arteritis. J Neuroophthalmol. 2014;34(3):243–5.
28. Kline LB, Hoyt WF. The Tolosa-Hunt syndrome. J Neurol Neurosurg Psychiatry. 2001;71:577–82.
29. Yeh C, Liao W. Multiple cranial nerve palsies caused by varicella zoster virus in the absence of rash. Neurol Asia. 2016;21(1):93–5.
30. Papgeorgiou E, et al. Fourth cranial nerve palsy and bilateral acute retinal necrosis following human herpesvirus 6 infection of the central nervous system. Ocul Immunol Inflamm. 2014;22(3):228–32.

31. Choi K, Park S. Petrositis with bilateral abducens nerve palsies complicated by acute otitis media. Clin Exp Otorhinolaryngol. 2014;7(1):59–62.
32. Srikanth SG, Taly AB, Nagarajan K, Jayakumar PN, Patil S. Clinicoradiological features of tuberculous meningitis in patients over 50 years of age. J Neurol Neurosurg Psychiatry. 2007;78(5):536–8.
33. Moghtaderi A, Alavi-Naini R, Rashki S. Cranial nerve palsy as a factor to differentiate tuberculous meningitis from acute bacterial meningitis. Acta Med Iran. 2013;51(2):113–8.
34. Halperin J. Nervous system Lyme disease. Curr Infect Dis Rep. 2015;17:445.
35. Kan L, Sood SK, Maytal J. Pseudotumor cerebri in Lyme disease: a case report and literature review. Pediatr Neurol. 1998;18:439–41.
36. Gilhus N, Verschuuren J. Myasthenia gravis: subgroup classification and therapeutic strategies. Lancet Neurol. 2015;14:1023–36.
37. Howard F, et al. Clinical correlations of antibodies that bind, block or modulate human acetylcholine receptors in myasthenia gravis. Ann N Y Acad Sci. 1987;505:526–38.
38. Howard F, Lennon V, Finley J, Matsumoto J, Elveback L. Clinical correlations of antibodies that bind, block or modulate human acetylcholine receptors in myasthenia gravis. Ann N Y Acad Sci. 1987;505:526–38.
39. Sarrigiannis P, et al. Single-fiber EMG with a concentric needle electrode: validation in myasthenia gravis. Muscle Nerve. 2005;3(1):61–5.
40. Gilhus N, et al. Myasthenia gravis – autoantibody characteristics and their implications for therapy. Nat Rev Neurol. 2016;12:259–68.
41. Wolfe GI, et al. Randomized trial of thymectomy in myasthenia gravis. N Engl J Med. 2016;375(6):511–22.
42. Salloway S, et al. Miller-Fisher syndrome associated with *Campylobacter jejuni* bearing lipopolysaccharide molecules that mimic human ganglioside GD3. Infect Immun. 1996;64(80):2945–9.
43. Wakerley B, Uncini A, Yuki N. Guillain-Barré and Miller Fisher syndromes – new diagnostic classification. Nat Rev Neurol. 2014;10:537–44.
44. Elder C, et al. Isolated abducens nerve palsy: update on evaluation and diagnosis. Curr Neurol Neurosci Rep. 2016;16(69):1–7.
45. Nallasamy N, Lesniak S, Volpe N, Tamhankar M. Unusual presentations of cavernous carotid aneurysms: further evidence for topographic organization of the oculomotor nerve. J Neurol Sci. 2010;295:82–6.
46. Müri RM, Chermann JF, Cohen L, et al. Ocular motor consequences of damage to the abducens nucleus area in humans. J Neuroophthalmol. 1996;16:191–5.
47. Volpe N, Lessell S. Remitting sixth nerve palsy in skull base tumors. Arch Ophthalmol. 1993;111(10):1391–5.
48. Frassanito P, et al. Recurrent and self-remitting sixth cranial nerve palsy: pathophysiological insight from skull base chondrosarcoma, report of 2 cases. J Neurosurg. 2013;12(6):633–6.
49. Chou KL, Galetta SL, Liu GT, Volpe NJ, Bennett JL, Asbury AK, Balcer LJ. Acute ocular motor mononeuropathies: prospective study of the roles of neuroimaging and clinical assessment. J Neurol Sci. 2004;219:35–9.
50. Murchison AP, Gilbert ME, Savino PJ. Neuroimaging and acute ocular motor mononeuropathies. A prospective study. Arch Ophthalmol. 2011;129:301–5.
51. Volpe N, Lee A. Do patients with neurologically isolated ocular motor cranial nerve palsies require prompt neuroimaging? J Neuroophthalmol. 2014;34(3):301–5.
52. Mehta S, Loevner LA, Mikityansky I, Langlotz C, Ying GS, Tamhankar MA, Shindler KS, Volpe NJ. The diagnostic and economic yield of neuroimaging in neuro-ophthalmology. J Neuroophthalmol. 2012;32:139–44.
53. Muthukrishnan J, Bharadwaj M, Singh Y. Isolated fourth cranial nerve palsy due to pituitary macroadenoma. Med J Armed Forces India. 2016;72:567–9.
54. Kontzialis M, et al. High-resolution3D magnetic resonance imaging of the sixth cranial nerve: anatomic and pathologic considerations by segment. J Neuroophthalmol. 2015;35:412–25.

55. Demer J, et al. High resolution magnetic resonance imaging demonstrates abnormalities of motor nerves and extraocular muscles in patients with neuropathic strabismus. J AAPOS. 2006;10(2):135–42.
56. Seitz J, et al. MR imaging of cranial nerve lesions using six different high-resolution T1 and T2-weighted 3D and 2D sequences. Acta Radiol. 2002;42:340–53.
57. Kau H, Tsai C, Ortube M, Demer J. High-resolution magnetic resonance imaging of the extraocular muscles and nerves demonstrates various etiologies of third nerve palsy. Am J Ophthalmol. 2006;143(2):280–7.
58. Sclocco R, et al. Challenges and opportunities for brainstem neuroimaging with ultrahigh field MRI. NeuroImage. 2018;168:412–26.
59. Gizewski E, et al. High-resolution anatomy of the human brain stem using 7-T MRI: improved detection of inner structures and nerves? Neuroradiology. 2014;56:177–86.
60. Yoshino M, et al. Visualization of cranial nerves using high-definition fiber tractography. Neurosurgery. 2016;79(1):146–65.
61. Tamhankar M, Ying G, Volpe N. Prisms are effective in resolving diplopia from incomitant, large and combined strabismus. Eur J Ophthalmol. 2012;22(6):890–7.
62. Whitecross S. Orthoptic management of incomitant strabismus. Int Ophthalmol Clin. 2014;54(3):83–8.
63. Tamhankar MA, Ying GS, Volpe NJ. Effectiveness of prisms in the management of diplopia in patients due to diverse etiologies. J Pediatr Ophthalmol Strabismus. 2012;49(4):222–8.
64. Tamhankar MA, Ying GS, Volpe NJ. Success of prisms in the management of diplopia due to fourth nerve palsy. J Neuroophthalmol. 2011;31(3):206–9.