

Infectious ophthalmoplegias

Rajeev Ranjan, Deependra Singh, Karthik Vinay Mahesh, Aastha Kapila Takkar, Sucharita Ray, Vivek Lal*

Department of Neurology, Postgraduate Institute of Medical Education and Research, Chandigarh 160012, India

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ABSTRACT

Though infections account for a significant proportion of patients with ocular motor palsies, there is surprising paucity of literature on infectious ophthalmoplegias. Almost all types of infectious agents (bacteria, viruses, fungi and parasites) can lead to ocular motor palsies. The causative infectious agent can be diagnosed in most cases using an orderly stepwise approach. In this review we discuss how to approach a patient with ophthalmoplegia with main focus on infectious etiologies.

1. Introduction

To examine a patient with ophthalmoplegia is the neurologist's delight for the simple reason that a careful neurological examination is often enough to provide a) exact anatomical localization in almost all and b) etiological diagnosis in most of the patients. Though infections account for a sizeable percentage of ophthalmoplegias especially in the developing world, the literature is surprisingly scarce with respect to infectious ophthalmoplegias. While infections are a less common cause of isolated ocular motor neuropathies in the outpatient setting in the western world, their frequency as cause of ophthalmoplegia is more robust among patients with multiple cranial nerve palsies and with other focal neurolog deficits. In the developing world, infections remain an important cause of ocular motor palsies both in isolation and combination with other neurological deficits. In this review, we discuss various infectious causes of ophthalmoplegias. As the type of infection varies with the site of lesion responsible for the ophthalmoplegia, we first discuss anatomical localization of the ophthalmoplegia, followed by possible infectious causes at each anatomical site and various clinical patterns which could lead to a specific etiological diagnosis.

2. Ophthalmoplegia: Where is the lesion?

The first step in evaluating a patient with suspected infectious ophthalmoplegia (as is true for any ophthalmoplegia) is to precisely localize the exact site of lesion clinically. This is especially important in cases of infectious ophthalmoplegias as type of infection varies with site of lesion. For example infectious ophthalmoplegias due to cavernous sinus

pathology are likely to result from either mucormycosis or aspergillosis, while multiple cranial nerve palsies due to lesions in subarachnoid space are more likely to be related to tuberculous meningitis. Thus, before proceeding further, we briefly discuss the anatomical localization of the ophthalmoplegia.

2.1. Ocular motor nuclei

Ocular movements are controlled by brainstem nuclei namely the oculomotor (3rd cranial nerve), trochlear (4th cranial nerve) and abducens (6th cranial nerve) nuclei. The abducens nerve nucleus innervates the lateral rectus (LR) muscle while the trochlear nerve nucleus innervates the superior oblique (SO) muscle. Oculomotor nerve nucleus providing the innervation of the medial rectus (MR), inferior rectus (IR), and inferior oblique (IO) muscles on same the side and superior rectus (SR) muscles on the contralateral side [1]. In addition one single caudal subnucleus (part of 3rd nerve nuclear complex) supplies both levator palpebrae superioris (LPS).

2.1.1. Lesions of 3rd nerve- anatomical localization

The third nerve nuclear complex consists of four paired nuclei and one unpaired nucleus (Fig. 1). The unpaired nucleus lies in the most dorsal location and consists of the Edinger Westphal nucleus (for pupillary constriction) and the nucleus for the LPS. Among paired nuclei, the most medial one supplies the contralateral SR through decussating fibers which traverse the contralateral SR subnucleus. Thus, nuclear third nerve lesions invariably result in bilateral eyelid ptosis and bilateral affection of SR [1–3]. Remaining three unpaired nuclei lie lateral to SR

* Corresponding author.

E-mail address: vivekl44@yahoo.com (V. Lal).

subnucleus. Out of these, the dorsal subnucleus supplies the IR (inferior rectus), while the intermediate subnucleus supplies the inferior oblique (IO). Neurons constituting the medial rectus (MR) subnucleus in addition to lying ventrally are also found scattered in two other areas of 3rd nerve nuclear complex. Accordingly isolated complete paralysis of the MR is

almost never due to nuclear 3rd nerve lesions [4]. Given the structure of the 3rd nerve nuclear complex (single unpaired nucleus for the LPS, pupillary constrictors and fibers for SR traversing opposite SR nucleus), it is clear that unilateral weakness of the LPS, SR and pupillary constrictors is highly unlikely due to lesions of 3rd nerve nucleus [1]. Looking at the

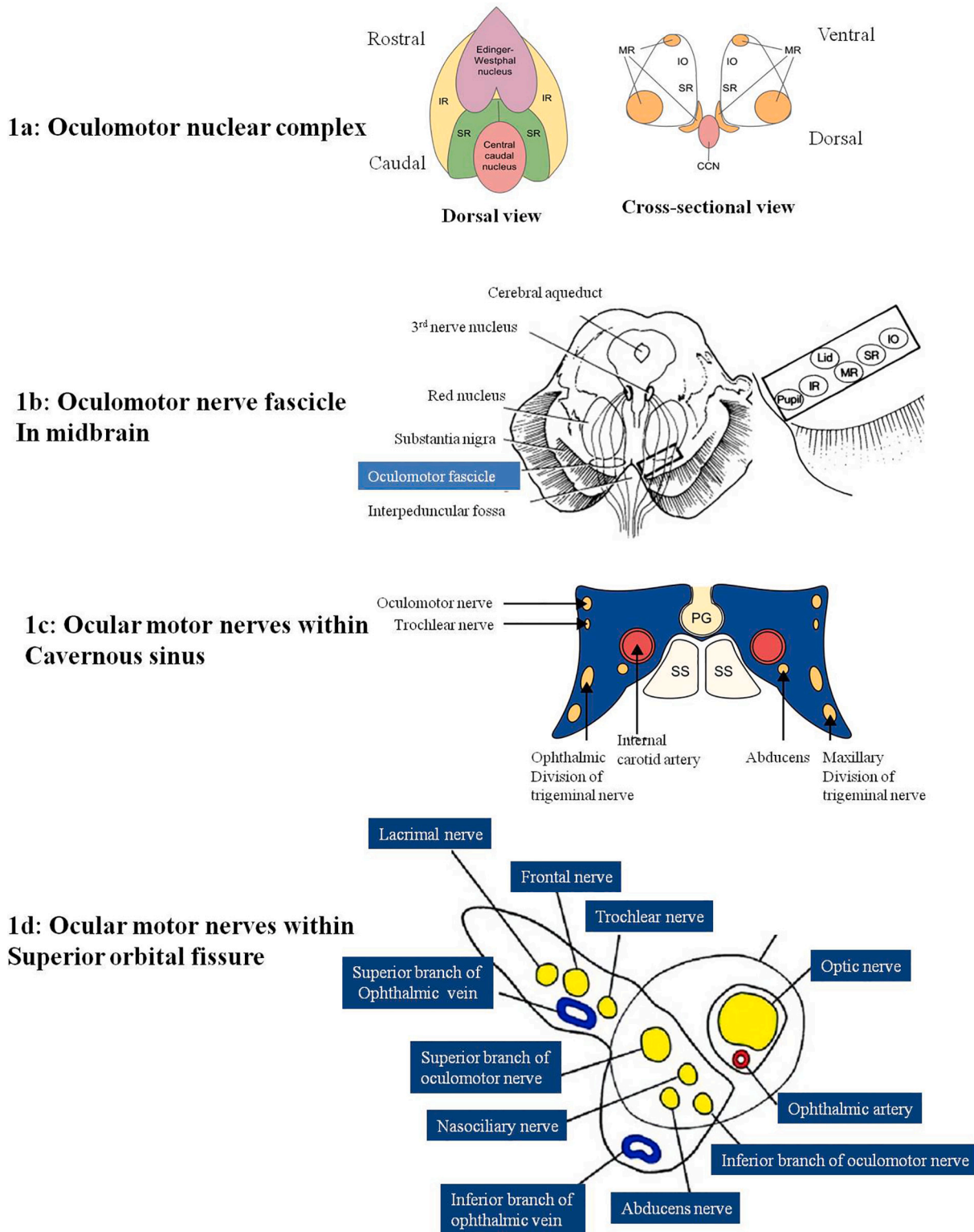


Fig. 1. Localization of lesion of 3rd cranial nerve. 1a: 3rd nerve nuclear complex; note that MR neurons are distributed at three different sites within nuclear complex; 1b: Oculomotor fascicle within midbrain and distribution of fibers for individual ocular muscles within fascicle; 1c and d: Relations of ocular motor nerves within cavernous sinus and superior orbital fissure respectively.

Abb: SR- superior rectus; MR- medial rectus; IR- inferior rectus; IO- inferior oblique; CCN- Central caudal nucleus; SS- sphenoid sinus; PG- pituitary gland.

structure of the nuclear complex, unilateral palsies of IR and IO muscles may rarely occur following small lesion of 3rd nerve nuclear complex. However in clinical practice isolated palsy of the IO and IR is almost always associated with lesions of orbit or ocular muscles. Other clinical patterns which may be seen with isolated nuclear complex lesions of the 3rd cranial nerve include

- i. Bilateral 3rd nerve palsy with normal lid elevation due to sparing of the caudal subnucleus [5,6]
- ii. Bilateral eyelid ptosis alone (affection of caudal subnucleus alone) [1]

The emanating fibers from the 3rd nerve nucleus form the 3rd nerve fasciculus which pass through the midbrain substance before emerging from the ventral aspect of the midbrain. *Pure fascicular lesions result in ipsilateral palsy of all muscles innervated by the 3rd cranial nerve.* Fibers for individual ocular muscles are arranged in the 3rd nerve fascicle in a topographic fashion (Fig. 1). The fibers for the IO muscle lie most laterally followed by the fibers for SR, MR, LPS, IR and the pupils in that order. The fibers for the pupillary constrictors lie most superior followed by IR, IO, MR, SR and LPS in that order. Accordingly small lesions of the oculomotor fascicle may affect individual ocular muscles [1]. As it traverses the midbrain, 3rd nerve fasciculus comes in close contact with the medial longitudinal fasciculus (MLF), the decussating fibers of superior cerebellar peduncle, the red nucleus and then the cerebral peduncles. *Accordingly pure fascicular 3rd nerve lesions are rare and nearly always associated with long tract signs due to involvement of various descending and ascending tracts in brainstem as reflected by clinical constellation of signs in Claude syndrome, Weber syndrome and Benedikt syndrome [1].*

After emerging from the midbrain, the 3rd cranial nerve courses forward in the subarachnoid space lying between the superior cerebellar and the posterior cerebral arteries. Here it is liable to compression by aneurysms. As the pupillary fibers lie in the outermost part of 3rd nerve, pupillary dilatation occurs 1st with compressive lesions of the 3rd nerve. On the other hand, ischemic lesions of the 3rd nerve in the subarachnoid space are likely to spare the outermost pupillary fibers and result in pupillary sparing 3rd nerve palsy [7].

The 3rd cranial nerve leaves the subarachnoid space by piercing the dura lateral to the posterior clinoid process and enters the lateral wall of cavernous sinus (CS). Here it lies in the close relation with the 4th, 5th (V1 in anterior, middle and posterior parts of the CS, V2 in middle and posterior part and V3 in the posterior part of CS) and 6th cranial nerves (Fig. 1). *Thus CS lesions usually affect multiple ocular motor nerves and the sensory divisions of the 5th nerve in varying combinations [1].*

Thereafter, the oculomotor nerve enters the orbit through the superior orbital fissure (SOF) (Fig. 1). Here, it divides into a superior division which supplies the SR and the LPS and an inferior division which supplies the MR, IR, IO, sphincter pupillae and the ciliaris muscles. *The clinical features of SOF syndrome are similar to an anterior CS syndrome.* At

the orbital apex, various ocular motor nerves come in close contact with the optic nerve. *Accordingly, visual impairment is used to distinguish CS/SOF lesions from an orbital apex syndrome [1].*

2.2. Lesions of the 4rd nerve- anatomical localization

Nucleus of the 4th cranial nerve lies inferior to the 3rd nerve nuclear complex at the level of inferior colliculus. Its fascicles run posteriorly around the aqueduct and decussate in the dorsal region of the midbrain to emerge from the dorsal aspect of the midbrain. 4th cranial nerve is unique as it is the only cranial nerve to emerge from the dorsal aspect of the brainstem [8,9] (Fig. 2). A lesion before its decussation will result in palsy of the contralateral SO while a lesion after the decussation will result in palsy of the ipsilateral SO. However in practice isolated 4th nerve palsy is practically never due to a brainstem lesion. Lesions of the fascicle or nucleus are usually associated with other brainstem signs (Table 1) such as a Horner syndrome (due to involvement of sympathetic fibers) [10] or ipsilateral internuclear ophthalmoplegia (due to involvement of medial longitudinal fasciculus) [11] or contralateral relative afferent pupillary defect (RAPD) (involvement of brachium of superior colliculus) [12] or ipsilateral dysmetria or ataxia (superior cerebellar peduncle). Lesions of the anterior medullary velum will result in bilateral 4th cranial nerve palsies [13].

After emerging from the brainstem, 4th cranial nerve runs anteriorly in the subarachnoid space in the quadrigeminal, ambient and the pontomesencephalic cisterns before piercing the dura to enter the CS just below the entry of the 3rd cranial nerve [9]. Lesions here will affect the 4th cranial nerve alone or with other cranial nerves in varying combinations. Here the, 4th nerve palsy may be associated with ipsilateral cerebellar signs (due to the lesions of superior cerebellar peduncle as the nerve runs anterolaterally around the midbrain) or contralateral hemiparesis mainly affecting the leg (due to involvement of the cerebral peduncle as nerve winds around it) [1]. In the CS, it lies in its lateral wall just below the 3rd cranial nerve and above the ophthalmic division of the 5th cranial nerve [14]. It enters the orbit through the SOF with the other ocular motor nerves and supplies the SO. Lesions in the CS or SOF or the orbital apex can be identified by associated cranial nerve palsies as described in section on anatomical localization of 3rd cranial nerve lesions. Within the orbit, lesions affecting the SO muscles are more likely to result in the SO palsy compared to lesions of the 4th cranial nerve [15].

2.2.1. Lesions of the 6th nerve- anatomical localization

The nucleus of the 6th cranial nerve lies in the dorsal pons separated from the floor of the 4th ventricle by the facial colliculus (genu of facial nerve). Within the 6th nerve nucleus, motor neurons which supply the LR are intermixed with the internuncial neurons whose axons cross the midline and run in the opposite MLF to supply the contralateral MR. Thus a lesion of the 6th nerve nucleus is invariably associated with

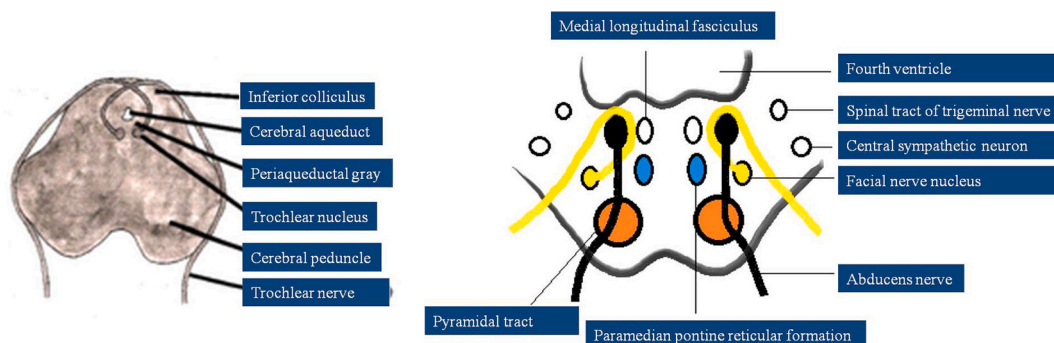


Fig. 2. Course of 4th and 6th cranial nerves in brainstem. 2a: Fourth cranial nucleus and nerve as it winds around midbrain; 2b: Sixth cranial nerve nucleus and its fasciculus. Note relations of sixth nerve fascicle as it passes through pons.

Table 1
Anatomical localization of ocular motor nerve lesions.

Localization of 3rd nerve lesions	
Site	Clinical features
Brainstem- at level of 3rd nerve nucleus	<i>3rd nerve nucleus</i> - ipsilateral complete 3rd nerve palsy with contralateral involvement of superior rectus and levator palpebrae superioris (LPS) <i>3rd nerve subnucleus</i> - palsy of individual muscles- inferior rectus (IR)/inferior oblique (IO) <i>Levator subnucleus</i> - bilateral ptosis alone
Brainstem – 3rd nerve fascicle	<i>Fascicle alone</i> - ipsilateral partial or complete 3rd nerve palsy <i>Fascicle + red nucleus (RN) + superior cerebellar peduncle (SCP)</i> - ipsilateral 3rd nerve palsy with contralateral ataxia and tremor (Claude syndrome) <i>Fascicle + RN/substantia nigra</i> - ipsilateral 3rd nerve palsy with contralateral chorea (Benedikt syndrome) <i>Fascicle + cerebral peduncle</i> - ipsilateral 3rd nerve palsy + contralateral hemiplegia (Weber syndrome) <i>Paramedian midbrain</i> (ipsilateral LPS fascicle and inhibitory pathways projecting on contralateral LPS)- ipsilateral ptosis and contralateral lid retraction (plus minus lid syndrome)
Subarachnoid space	Partial/complete 3rd palsy with or without other cranial nerve palsies
Cavernous sinus (CS)	Partial/complete 3rd nerve palsy with or without involvement of 5th cranial nerve (V1/V2 divisions), 4th and 6th cranial nerves or ocular sympathetic fibers
Superior orbital fissure (SOF)	Same as CS but without Horner's; proptosis is often present
Orbital apex	Same as SOF but with additional optic nerve (ON) involvement leading to vision loss
Orbit	Palsy of superior or inferior division of 3rd cranial nerve, visual loss (ON), proptosis, chemosis, eyelid swelling etc.
Localization of 4th nerve lesions	
Site	Clinical features
Brainstem- nucleus/fascicle	<i>Anterior medullary velum</i> - bilateral 4th cranial nerve palsies <i>Fascicle + SCP</i> - ipsilateral dysmetria + contralateral SO palsy <i>Fascicle + descending sympathetic tract</i> - ipsilateral Horner's syndrome + Contralateral SO palsy <i>Fascicle + superior colliculus brachium</i> - contralateral SO palsy + contralateral relative afferent pupillary deficit <i>Fascicle + medial longitudinal fasciculus (MLF)</i> - ipsilateral internuclear ophthalmoplegia + contralateral palsy of SO muscle <i>Nucleus/fascicle alone</i> - isolated 4th cranial palsy (very rare)
Subarachnoid space	<i>4th cranial nerve alone</i> - isolated 4th cranial nerve palsy <i>4th cranial nerve + SCP</i> - ipsilateral SO palsy and dysmetria <i>4th cranial nerve + cerebral peduncle</i> - ipsilateral SO palsy and contralateral hemiplegia
Cavernous sinus	4th nerve palsy with or without involvement of 5th cranial nerve (V1/V2 divisions), 3th and 6th cranial nerves or ocular sympathetic fibers
Superior orbital fissure	Same as CS but without Horner's; proptosis is often present
Orbital apex	Same as SOF but with additional optic nerve (ON) involvement leading to vision loss
Orbit	Palsy of 4th cranial nerve, visual loss (ON), proptosis, chemosis, eyelid swelling etc.
Localization of 6th cranial nerve lesions	
Site	Clinical features
Brainstem- nucleus	<i>6th nerve nucleus alone</i> : Ipsilateral gaze palsy <i>6th cranial nerve + 7th cranial nerve + cerebellar peduncle</i> - ipsilateral gaze palsy + ipsilateral facial palsy and ipsilateral dysmetria
Brainstem- fascicle	<i>6th cranial nerve + 7th cranial nerve + corticospinal tract</i> - ipsilateral gaze palsy + ipsilateral facial palsy and contralateral hemiparesis (Millard- Gubler syndrome) <i>Fascicle alone</i> - isolated 6th nerve palsy (very rare)
Subarachnoid space	

Table 1 (continued)

Localization of 3rd nerve lesions	
Site	Clinical features
	<i>6th cranial nerve fascicle</i> - 6th cranial nerve palsy alone or with other cranial nerve palsies in varying combinations <i>6th cranial nerve + corticospinal tract</i> - ipsilateral 6th cranial nerve palsy and contralateral hemiparesis <i>6th cranial nerve + 5th nerve</i> - ipsilateral 6th cranial nerve + facial (especially retro-orbital) pain with or without deafness (Gradenigo syndrome)
Petrous apex	6th nerve palsy with or without involvement of 5th cranial nerve (V1/V2 divisions), 3th and 4th cranial nerves or ocular sympathetic fibers Parkinson syndrome- ipsilateral 6th cranial nerve palsy + Horner syndrome
Cavernous sinus	Same as CS but without Horner's; proptosis is often present
Superior orbital fissure	Same as SOF but with additional optic nerve (ON) involvement leading to vision loss
Orbital apex	Palsy of 6th cranial nerve, visual loss (ON), proptosis, chemosis, eyelid swelling etc.
Orbit	

anipsilateral gaze palsy. Thereafter axons of the 6th nerve nucleus form the 6th cranial nerve fasciculus which runs anteriorly through the substance of the pons to emerge from the brainstem between the pons and medulla. During its course through the brainstem 6th cranial nerve axons pass in close contact with the medial lemniscus and lies medial to the 7th cranial nerve, while during emergence from the brainstem, these lies lateral to the corticospinal tract. Thus a lesion of the 6th nerve fasciculus is often associated with ipsilateral 7th nerve palsy, ipsilateral dysmetria or contralateral hemiparesis [1] (Fig. 2). Thereafter the 6th cranial nerve runs in close association with the 5th nerve in the Dorello canal at the petrous apex. A lesion here often results in ipsilateral facial (retro-orbital) pain and deafness in addition to 6th cranial nerve palsy. Thereafter the 6th cranial nerve enters the CS. Within the CS, the 6th cranial nerve is joined by ocular sympathetic fibers for few a millimeters. A lesion here results in Parkinson syndrome (ipsilateral 6th cranial nerve palsy and Horner's syndrome) [1,16]. Thereafter the 6th cranial nerve enters the orbit through the SOF and ends by supplying the LR. Localization of lesions within the CS, SOF and orbit has been discussed in section 2.2.1 (Table 1).

To understand the clinical value of the anatomical localization discussed above, a hypothetical clinical situation is being discussed below. A person with isolated 3rd nerve palsy can have lesion anywhere along the course of the 3rd nerve. Now if the same person has bilateral eyelid ptosis in addition to unilateral complete 3rd nerve palsy, the localization of lesion will change to the brainstem at the level of the 3rd nerve nucleus. The presence of associated long tract signs will put the site of lesion to the brainstem around the 3rd nerve fascicle. The presence of cranial nerve palsies other than ocular motor nerves will localize lesion to the skull base or suggest an infiltrative pathology of the subarachnoid space or a diffuse meningeal disease (e.g. lymphoma, hypertrophic pachymeningitis etc.). Involvement of ocular motor nerves in varying combination with the first or second division of the 5th cranial nerve and/or ocular sympathetic will localize lesion to the CS. The presence of proptosis in the absence of Horner's syndrome will localize the lesion to the SOF while presence of vision loss will suggest a lesion at the orbital apex. Paralysis of individual ocular muscles suggest an ocular muscle lesions as cause of disease while bilateral ocular motor palsies without pupillary involvement or sensory symptoms will localize the lesion to the ocular muscles or the neuromuscular junction.

In a similar way, a precise anatomical localization of lesions affecting the 4th or 6th cranial nerves can also be obtained.

3. Infectious causes of ophthalmoplegia

The common infectious causes of ophthalmoplegia at every anatomical level of localization are enumerated in Table 2.

4. Common causes of infectious ophthalmoplegia

4.1. Meningitis

The term meningitis or more specifically “leptomeningitis” is used to denote infection of the meninges and the subarachnoid space. The inflammatory process often extends from the meninges to involve the brain and spinal cord. In addition, inflammation of the subarachnoid space may result in damage to blood vessels and cranial nerves during their course in subarachnoid space. Meningitis due to infectious agents is classified further into acute and chronic meningitis. The clinical picture of acute meningitis is quite dramatic with fever, headache, vomiting, altered mental status and meningeal signs. Acute infectious meningitis only rarely result in ocular motor palsies per se. Usually ocular motor palsies seen in acute pyogenic meningitis are secondary to complications such as brainstem infarction and raised intracranial pressure(ICP), etc. [17,18]. Chronic meningitis, on the other hand, is often associated with ocular motor palsies [19]. Chronic meningeal inflammation with attendant exudation often leads to extensive fibrosis in the subarachnoid space with entrapment and compression of cranial nerves. In addition, obliterative endarteritis secondary to meningeal inflammation can cause nerve ischemia and infarction. Other causes of ocular motor palsies in chronic meningitis include brainstem infarcts, granulomas or abscesses as well as nerve damage due to ICP [19].

Diagnosis of infectious meningitis relies on CSF analysis as well as neuroimaging findings.

Certain specific patterns on neuroimaging especially brain magnetic resonance imaging (MRI) may give diagnostic cues towards presence of

Table 2
Common infectious causes of ophthalmoplegias at different anatomical locations.

Anatomical site	Infectious cause
Brainstem	Tuberculoma, Neurocysticercosis, Listeria, Bacterial abscess, Fungal granuloma/abscess, syphilitic gumma, Toxoplasma
Subarachnoid space	Brainstem infarcts due to infectious meningo-vasculitis Meningitis [tuberculous, pyogenic, fungal including cryptococcal, viral (human immunodeficiency virus, cytomegalovirus, Epstein Barr virus) parasitic (neurocysticercosis), syphilitic, etc.], Neuroborreliosis, Lyme disease
Cavernous sinus (CS)	Fungal infect ions (aspergillosis, mucormycosis, others), Bacterial sinusitis with adjacent CS affection Skull base osteomyelitis (bacterial, fungal, tubercular) spreading to CS Tuberculosis Cavernous sinus thrombosis due to bacterial infection Bacterial, fungal or tubercular involvement of pituitary with affection of adjacent CS
Superior orbital fissure (SOF)	Fungal infect ions (aspergillosis, mucormycosis, others), Bacterial sinusitis with adjacent CS affection Skull base osteomyelitis (bacterial, fungal, tubercular) spreading to CS Tuberculosis CS infection with spread to SOF
Orbit	Fungal infect ions (aspergillosis, mucormycosis, others) Pyogenic orbital cellulitis Bacterial sinusitis with spread to orbit Tuberculosis Others
Petrous apex for 6th cranial nerve	Otitis media or mastoiditis of bacterial/fungal/tubercular etiology
Unknown localization	Herpes (mainly for 3rd and 4th nerve), Lyme disease, Infectious mononucleosis etc.

a specific infection. However, more often than not, CSF analysis is needed for confirmatory diagnosis. Whenever possible, CSF should be obtained and sent for detailed analysis including total and differential cell counts, glucose and protein levels, gram, Zeihl Neelsen and Indian Ink staining as well as bacterial and fungal cultures. In addition, PCR for *Mycobacterium tuberculosis*, herpes simplex virus, antigen testing for cryptococcus, meningococcus and pneumococcus as well as Pan viral PCR and PCR for organisms such as listeria may be carried out wherever indicated. Management includes treatment directed at underlying infectious agent. However in absence of confirmatory diagnosis, empirical treatment may be initiated depending upon etiological profile of meningitis in a particular region [19]

4.2. Encephalitis

Unlike meningitis, encephalitis is characterized by inflammation within the brain parenchyma. However in most of infectious cases, the meninges and the brain parenchyma are affected together and the process is then called meningoencephalitis. Infectious encephalitis is a catastrophic disease characterized by fever, headache, vomiting, seizures, focal deficits and altered mental status ranging from drowsiness to coma. Ocular motor palsies are not very common in infectious encephalitis expect for one specific subgroup called rhombencephalitis or brainstem encephalitis [19,20]. As discussed under localization, brainstem encephalitis may result in ocular motor palsies through inflammatory or direct damage to ocular motor nuclei or their fascicles. Alternatively the nerves may get entrapped in the exudates as these emerge from the brainstem or run in the subarachnoid space. As discussed earlier, brainstem involvement is frequently reflected in these patients as motor deficits, sensory abnormalities, gaze palsies, INOs, alteration in conscious level, ataxia as well as breathing abnormalities and cardiac arrhythmias. Most common causes of rhombencephalitis include listeria, herpes virus and enterovirus 71. However it can result from many other bacteria, other viruses or even fungi. The mainstay of diagnosis of brainstem encephalitis continues to be CSF analysis, neuroimaging and mainstay of management continues to be treatment of underlying infectious agent [19,21].

5. Common infectious etiologies for ophthalmoplegia

5.1. Tuberculosis (TB)

Globally in 2020 alone, TB affected approximately 10 million people worldwide out of which 1% were due to central nervous system (CNS) TB. With such high numbers, it should not surprise the reader to find TB listed as the foremost cause in infectious ophthalmoplegias [22].

TB can affect the ocular motor nerves in several ways. It can affect ocular motor nuclei or their fascicles at the brainstem level due to direct affection by tuberculomas (Fig. 3) or abscess or due to brainstem infarctions secondary to meningo-vasculitis. The basal exudates secondary to tuberculous meningitis (TBM) can encase various ocular motor nerves resulting in compression, fibrosis and scarring (Fig. 4). Alternatively, ocular motor nerves may get damaged by ischemia secondary to tubercular vasculitis of the vasa nervosum which run in the subarachnoid space. Furthermore the 6th cranial nerve may be affected secondarily by the raised ICP. TB can affect ocular motor nerves through the CS or the SOF TB and can rarely cause ophthalmoplegia through direct affection of the ocular muscles as well [23,24].

Though visual loss in CNS TB has been well studied, there is lack of data regarding exact incidence and prognosis of ophthalmoplegia in TBM. In a study ($n = 209$) from our institute [25], ocular motor palsy was seen in 49 (23.4%) subjects. Isolated 6th cranial nerve involvement was seen in 35 (16.7%) patients. 6th nerve palsy was bilateral in 7/35 (20%) patients. Third cranial nerve palsy was seen in 5 (2.4%) patients out of whom one patient had bilateral involvement. Nine patients had both 3rd and 6th cranial nerve palsies. At follow-up of these patients

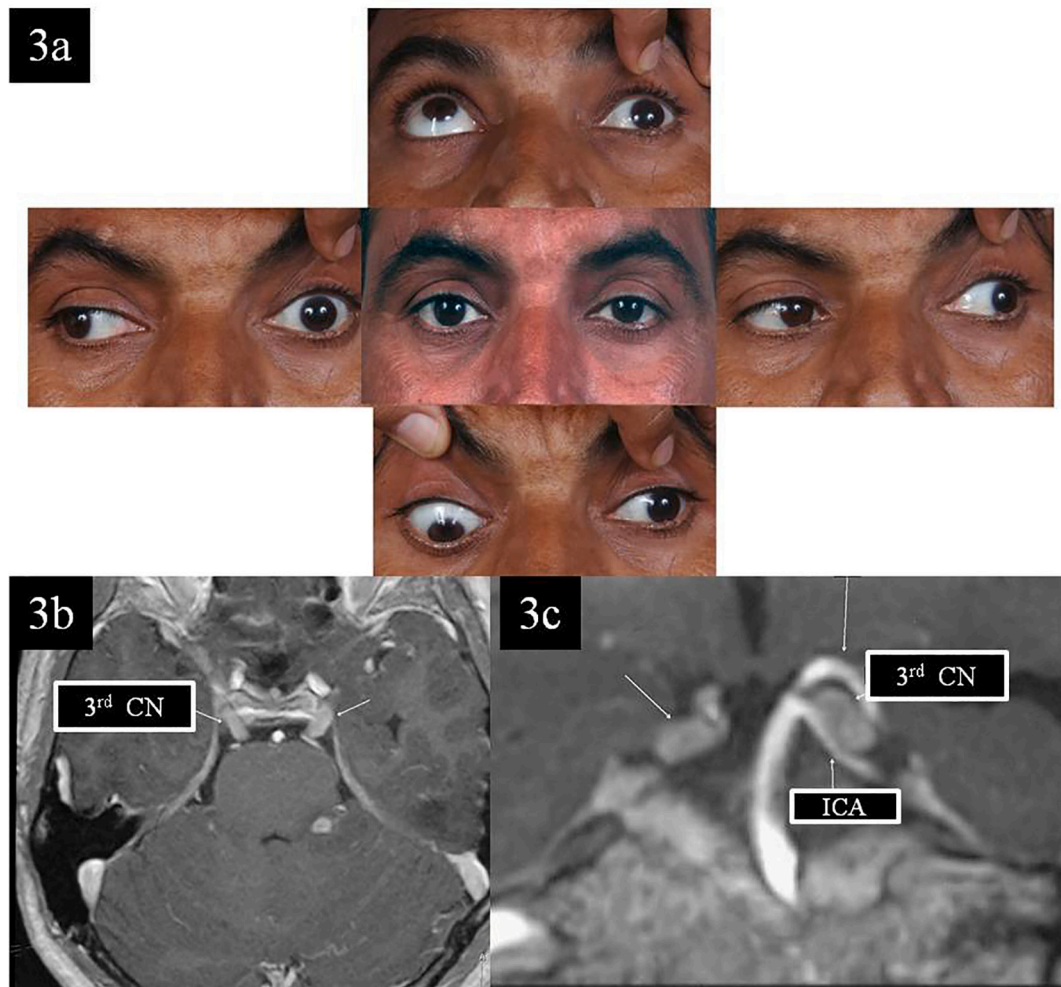


Fig. 3. Right oculomotor nerve palsy (3a) in a patient with tuberculous meningitis. Note bilateral thick and enhancing oculomotor nerves (white arrows) on Gadolinium enhanced T1 weighted magnetic resonance images (3b and 3c). Also note tuberculoma in prepontine cistern on left side (3b); Abb: CN- cranial nerve; ICA- internal carotid artery.

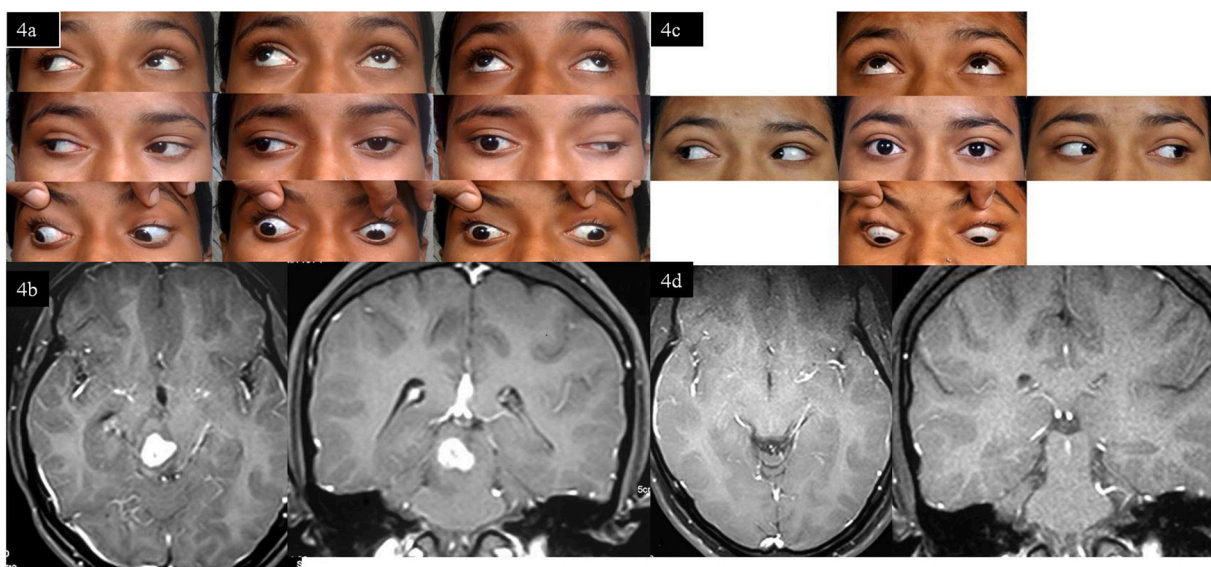


Fig. 4. Bilateral ptosis and right sided oculomotor nerve palsy in young girl (4a) with brainstem tuberculoma (4b); Note complete clinical (4c) and radiological recovery (4d) at three month follow up.

(unpublished data), cranial nerve palsies had recovered in more than 90% with proper treatment. TBM should be suspected in all patients who present with fever, headache and vomiting along with ocular motor palsies. The mainstay of diagnosis of TBM remains neuroimaging and cerebrospinal fluid (CSF) examination. Magnetic resonance imaging (MRI) of the brain typically shows enhancement of the leptomeninges and exudates with predilection for the perimesencephalic, interpeduncular, prepontine, and the suprasellar cisterns. MTR (magnetization transfer ratio) increases the sensitivity of diagnosis by better delineation of meningeal thickening on precontrast images and enhancement on post contrast images. MRI brain may also show brainstem infarcts or in other brain regions. In a study [26] from our center, brain MRI was abnormal in >95% of all patients with TBM. The confirmation of the diagnosis of CNS TB depends upon the isolation of *Mycobacterium tuberculosis* (MTB) from CSF or from brain biopsy samples. Routine CSF examination frequently shows lymphocytic pleocytosis, low glucose and high protein levels. In a study from our center [27], CSF culture was positive in approximately 25% of patients while CSF polymerase chain reaction (PCR) for MTB was positive in close to 70% of patients. The sensitivity of Xpert Ultra was 72% in CNS TB in a study from our center [28].

In contrast to TBM, the clinical presentation of brainstem tuberculomas (Fig. 4) and tubercular abscesses is less dramatic and symptoms and signs of meningeal inflammation such as fever, headache, neck stiffness, etc. may be inconspicuous or even absent. Accordingly their diagnosis rests on a high degree of suspicion and appropriate testing including Gadolinium enhanced brain MRI. Possibility of brainstem TB should be kept in mind in all patients with subacute onset brainstem syndrome even in absence of fever, headache and meningeal signs. MR features which suggest tuberculomas as cause of brainstem syndrome include iso to hypointense lesion with hyperintense rim on T1 weighted images and hypointense signal on T2 weighted images with irregular wall enhancement. Tubercular abscess can be identified by appearance of central hyperintensity in hypointense lesion on T2 weighted images. Other patterns which can be seen on MRI include miliary mottling (small ring enhancing lesions with hypointense center on T2 weighted images) and cerebritis [29]. However all these findings are non-specific and final diagnosis rests on biopsy or demonstration of MTB from a lesion in brain or in some other part of body. These imaging findings may nevertheless help to start empirical antitubercular treatment in appropriate clinical setting while awaiting results of more definitive diagnostic tests. Despite all diagnostic tests, definitive diagnosis is not possible in all cases and one has to rely on clinical judgment and response to antitubercular treatment for diagnosis [30].

Tubercular involvement of the CS and orbit is very rare. Diagnosis rests on strong clinical suspicion and demonstration of MTB either on direct biopsy of the brain lesion (if amenable) or demonstration of tubercular lesions elsewhere in the body. Mainstay of treatment continues to be antitubercular treatment with steroids [30].

5.2. Cryptococcal meningitis (CM)

Cryptococcal meningitis (CM) caused by *Cryptococcus neoformans* is the second most common opportunistic infection (after TB) in patients with acquired immune deficiency syndrome (AIDS) in Sub-Saharan Africa and South East Asia. It alone is responsible for 13–44% of deaths occurring among sub-Saharan African people living with human immunodeficiency virus infection (HIV) [31]. The most common clinical features include headache, fever, vomiting, malaise and alteration of mental status. Less common symptoms include cognitive decline, vision loss, focal neurological deficits and gait ataxia, etc. [32].

CM can affect ocular movements in many ways just like TBM. It can affect the ocular motor nuclei at the level of the brainstem through infarction secondary to meningovascularitis and rarely by compression through formation of cryptococcomas. Like TBM, it can affect ocular motor nerves at the level of the subarachnoid space through exudates

and obliterative endarteritis. However, most common cause of ocular palsy in CM is likely related to raised intracranial pressure (ICP) which occurs in approximately 75% [33]. An increase in ICP results in distortion of nerve structure in the subarachnoid space with consequent impairment of function. Due to its longest intracranial course, the abducens nerve is particularly sensitive to the effects of raised ICP.

Just like TBM, well conducted prospective studies evaluating ocular motor palsies in CM are rare, though there is good amount of literature regarding visual loss in CM. Thus, most information regarding ophthalmoplegia in CM is obtained from small case series and case reports. In one review, cranial nerve palsies other than optic nerve involvement were reported in 8% of patients with CM [19]. In a landmark article published in 1964 (pre HIV era), Okun and Butler [33] reported cranial nerve palsies in 5/36 (13.9%) patients with CM. Out of these five patients, two had bilateral 6th cranial nerve paresis, two had unilateral 6th cranial nerve paresis and one had bilateral 3rd cranial nerve paresis. In the post HIV era, Kestelyn et al. [34] reported abducens nerve palsy in 7/78 (9%) of patients with CM in AIDS. However both of these studies did not report on follow up of ocular motor palsies. Mao et al [35] reported abducens nerve palsy in 7.5% of patients with CM. Other findings related to ophthalmoparesis in CM include bilateral complete ophthalmoplegia, wall eyed bilateral INO (WEBINO), INO [36] and sequential involvement of 3rd, 4th and 6th cranial nerve palsies [37] as well as horizontal and vertical gaze palsies (due to brainstem infarctions) [36].

Diagnosis of CM rests on clinical suspicion and CSF analysis. CM should be suspected in all patients presenting with subacute or chronic meningitis irrespective of their immune status. Neuroimaging may reveal meningeal enhancement, cerebral edema, cryptococcomas, gelatinous pseudocysts (CSF intensity lesions seen most commonly in basal ganglia), hydrocephalus and brain infarctions. CSF reveals lymphocytic pleocytosis, low glucose and high protein content. Sensitivity of CSF India Ink staining in demonstration of cryptococcus ranges from 70 to 90% while that of CSF cryptococcal antigen test is close to 95% with almost 100% specificity. Gold standard for diagnosis of CM is demonstration of *Cryptococcus neoformans* in CSF though culture on (SDA) Sabouraud dextrose agar medium. Mainstay of treatment continues to be induction therapy with amphotericin B and flucytosine followed by consolidation therapy with fluconazole. Steroids are contraindicated in CM and mainstay of raised ICP remains repeated CSF drainage through serial lumbar punctures [19].

5.3. CNS infection with *Listeria*

Listeria monocytogenes, a gram positive bacterium, is the 4th leading cause of bacterial meningitis in the Western world accounting for 20% of bacterial meningitis in neonates and people above 60 years of age [38,39]. Unlike other bacterial meningitis, Listerial meningitis tends to have a subacute course, lower frequency of stiff neck (25%) and higher frequency of focal neurological deficits (35–40%), fluctuating mental status (75%), seizures (10–25%), normal CSF glucose (>60%), positive blood culture (50–75%) as well as movement disorders (15–20%). The importance of *Listeria monocytogenes* in a review on infectious ophthalmoplegias arises from its tendency to affect brainstem with associated ocular motor palsies, which is being discussed below.

5.3.1. Listerial rhombencephalitis

A peculiar feature of *Listeria monocytogenes* is its tendency to affect brainstem resulting in clinical syndrome of rhombencephalitis. Listerial rhombencephalitis occurs in 5–10% of all listerial infections. In contrast to listerial meningitis which typically affects immunocompromised individuals or at extremes of age, listerial rhombencephalitis affects otherwise healthy adults. Clinical course of Listerial rhombencephalitis involves two phases: a prodromal phase of fever, headache, nausea and vomiting lasting for 4–5 days followed by an acute, progressive phase of brainstem involvement with attendant cranial nerve palsies,

hemisensory signs, motor weakness and cerebellar ataxia [38]. In one systemic review ($n = 123$), the most common cranial nerve palsies were 7th cranial nerve (57.7%) followed by 5th (44.7%), 9th (40.7%) and 10th (39.8%) cranial nerves. Ocular motor palsies included 6th cranial nerve (35.8%) followed by 3rd (20.3%) and 4th cranial nerve (4.1%) [39]. In another review [40] involving 63 patients, 7th cranial nerve was most commonly affected ($n = 43$), followed by 6th cranial nerve ($n = 41$). 3rd and 4th cranial nerves were affected in 14 and six patients respectively. CSF glucose was normal in 79% of patients. Most patients (63%) had only mild (<100 mg/dl) elevation of CSF protein. CSF revealed lymphocytic pleocytosis of $<500/\mu\text{l}$ in most.

The mainstay for diagnosis of Listerial rhombencephalitis is avid clinical suspicion, suggestive clinical picture, neuroimaging especially brain MRI (Fig. 5) and blood as well CSF cultures and CSF PCR. Mainstay of management is Ampicillin in conjunction with a synergistic aminoglycoside. Mortality rate in Listerial rhombencephalitis continues to be high (30%) and approximately 60% of survivors are left with residual neurological sequelae [38–40].

5.4. Neurosyphilis

Neurosyphilis is a great mimicker and should be considered in the differential diagnosis of all subacute or chronic meningitis. Neurosyphilis is defined as confirmed if CSF VDRL (venereal disease laboratory test) is positive at any stage of syphilis. It is considered as presumptive in the presence of a) any syphilitic stage, b) nonreactive CSF VDRL, c) elevated CSF cell count or protein in the absence of other known causes and d) clinical picture consistent with neurosyphilis in the absence of other known causes.

Most of our information regarding ocular motor involvement in neurosyphilis comes from case reports or retrospective case series. Ocular motor palsies classically occur during the stage of syphilitic meningitis (secondary syphilis). These can result from exudates in the subarachnoid space either entrapping the nerve or causing arteritis with brainstem infarction as well as due to space occupying lesions in brainstem and other regions of brain called gummas [41]. There are several case reports of isolated oculomotor nerve palsy due to gumma formation on 3rd cranial nerve [42,43]. At times, neurosyphilis can present with abducens nerve palsy as well as gaze palsies as well [44–

46]. Accordingly diagnosis of neurosyphilis should be considered in any patient who present with ocular motor palsy in absence of other known causes and CSF examination including VDRL and TPHA (Treponema pallidum haemagglutination) tests should be carried out if considered necessary.

5.5. Viral causes of infectious ophthalmoparesis

Though several viruses like Epstein Barr virus, Enterovirus 71, herpes virus and cytomegalovirus etc. have been associated with ophthalmoparesis, two viruses (varicella zoster virus and SARS-CoV-2) require special mention and are being discussed here:

5.5.1. Varicella zoster (Fig. 6)

The lifetime risk of herpes zoster is approximately 30%. Herpes zoster ophthalmicus resulting from the reactivation of varicella zoster virus (VZV) affecting the ophthalmic division of the 5th nerve accounts for 10–20% of all herpes zoster cases. Neurological complications of herpes zoster include meningitis, meningoencephalitis, CNS vasculitis, myelitis and cranial neuritis [47,48].

Herpes zoster ophthalmicus may be associated with ocular motor palsies in 5–31% of all cases. The ocular motor palsies may be isolated or combined [49,50]. Various reasons postulated for ocular motor palsies include a) viral nerve invasion via hematogenous spread or trans-synaptic migration, b) perineuritis secondary to VZV and c) vasculitis induced by VZV and consequent nerve infarction. In addition, inflammation may spread from the ophthalmic nerve to the CSF or the SOF and then to the ocular motor nerves resulting in CSS or SOF syndrome. In some cases, the inflammation may spread from the 1st division of the 5th cranial nerve to the orbit and then to the orbital muscles resulting in orbital myositis. In fact there are several small series and case reports of orbital apex syndrome, orbital myositis and CSS after herpes zoster ophthalmicus. Edgerton AE in 1948 described four cases of unilateral ophthalmoplegia following herpes zoster ophthalmicus. Three out of these four patients improved completely at follow up [51]. Chhabra and Golnik [52] described 18 patients with ocular motor palsies following herpes zoster ophthalmicus. Six patients had isolated 6th nerve palsy, five had isolated 3rd nerve palsy alone, three had fourth nerve palsy alone, one had combined 3rd and 4th cranial nerve palsy, two had

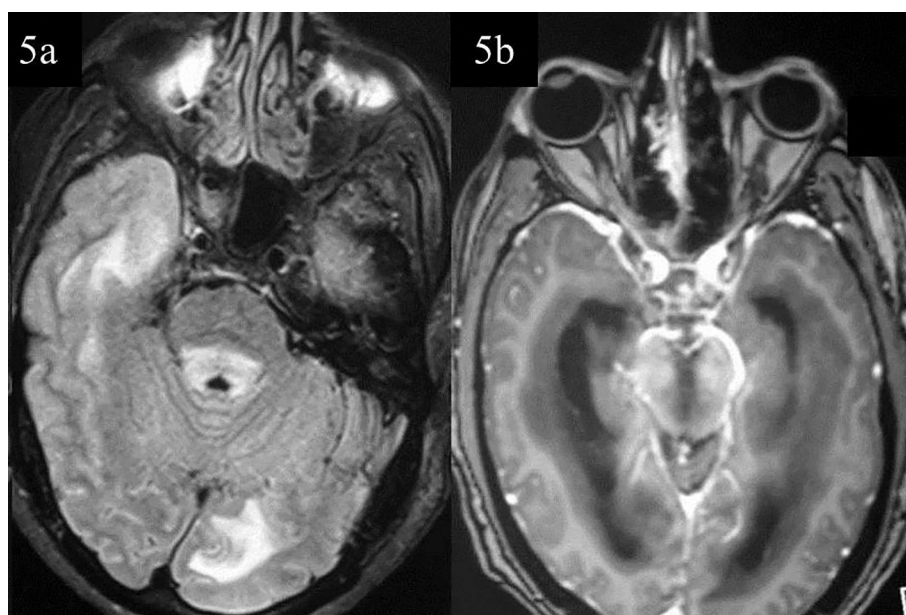


Fig. 5. Listerial rhombencephalitis in a 57 years old gentleman presenting with fever and altered sensorium of three days duration. Note: Brainstem signal changes with obstructive hydrocephalus on fluid attenuated inversion recovery sequences showing (5a) and thick enhancing exudates around brainstem on Gadolinium enhanced T1 weighted magnetic resonance images (5b).



Fig. 6. Right abducens nerve palsy in a 64 years old gentleman 15 days following an attack of herpes zoster.

combined 3rd and 6th nerve palsy and one had complete unilateral ophthalmoplegia. Mean duration between onset of herpes zoster ophthalmicus and ophthalmoplegia was 8.6 days (range 1–15 days). Mean age was 75 years and all patients were on antiviral treatment at the time of onset of ophthalmoplegia. 50% of the patients recovered completely at follow up. Several other authors have reported orbital apex syndrome as well as orbital myositis with attendant chemosis, proptosis, ptosis and ophthalmoplegia in association with herpes zoster ophthalmicus. In these patients, MRI of the orbits and CSF region may show enhancing orbital soft tissue, extraocular muscle enlargement, enhancing soft tissue in region of orbital apex, SOF or CS as well as enlarged lacrimal gland and enlarged and enhancing optic nerve sheath [51–55].

Evaluation of patients with ocular motor palsy secondary to herpes zoster ophthalmicus includes neuroimaging preferably gadolinium enhanced brain MRI and orbits plus CSF examination. CSF examination should include PCR testing for VZV DNA (deoxyribonucleic acid) and/or antibody titer for VZV. Management includes intravenous acyclovir in a dose of 10–15 mg/Kg every eight hourly for 2–3 weeks with or without oral steroids for 5 days. More than 90% of patients make full recovery by 6–12 months [19,51].

5.5.1.1. VZV vasculopathy. Another reason for ocular motor palsies including skew deviation and gaze paresis in VZV related illness is brainstem infarction. It results from vasculopathy secondary to trans-axonal spread of the virus from nerves to the arterial adventitia resulting in granulomatous transmural inflammation of the arterial wall with giant cell formation and intra-arterial thrombosis. After an episode of herpes zoster, the risk of ischemic stroke is increased by 30%. The risk of stroke after an episode of herpes zoster ophthalmicus is however, much higher and estimated to be 90%. This risk is maximal during the first 30 days after herpes zoster. VZV vasculopathy can affect both large and small vessels. While former are affected usually in immunocompetent patients, later are usually affected in immunocompromised individuals. The clinical picture includes transient ischemic attacks or stroke with attendant focal deficits including various brainstem syndromes, seizures, visual loss and alteration of mental status [56–58]. While diagnosis is easy in setting of recent rash, approximately 30–40% of patients may never develop rash or develop neurological symptoms after a long delay and accordingly present diagnostic difficulties. Diagnosis of VZV vasculopathy rests on avid clinical suspicion and appropriate diagnostic tests including CSF VZV DNA PCR (sensitivity/specificity >98%) and a

higher CSF VZV antibody levels compared to serum signifying intrathecal production of anti-VZV antibodies. Treatment includes intravenous acyclovir in a dose of 10–15 mg/Kg every eight hourly for 2–3 weeks with oral steroids for first 5 days.

5.5.2. SARS-CoV-2

Neurological manifestations related to SARS-CoV-2 virus are just beginning to get unfolded. While hyposmia, hypogeusia, stroke, skeletal muscle injury and alteration of mental status are already well known neurological manifestations of SARS-CoV-2 virus [59], the same cannot be said about ophthalmological complications. Nevertheless, case reports related to ophthalmic complications of SARS-CoV-2 have just started to come. At time of writing this article there are few case reports of ophthalmoparesis in association with SARS-CoV-2 infection.

Pascual-Goñi et al. [60] described two patients with ophthalmoparesis following COVID 19 infection. Their first patient was a 60 year old woman who presented with headache and diplopia, 10 days after fever, cough and hyposmia. Examination revealed a right 6th cranial nerve palsy. Nasopharyngeal swab revealed presence of SARS-CoV-2 RNA. CSF was normal and negative for SARS-CoV-2 RNA. MRI revealed signal changes in the pontine tegmentum and the right 6th cranial nerve nucleus, mamillary bodies and hypothalamus as well as enlarged pituitary gland and pituitary stalk. The second patient was a 35 years- old lady who presented with diplopia and paresthesias following an episode of bulimia and vomiting. Later she developed progressive encephalopathy with inattention, drowsiness, bilateral 6th cranial nerve palsies and paraparesis. She never had fever or chest symptoms. Nasopharyngeal swab revealed presence of SARS-CoV-2 RNA. CSF was normal and negative for SARS-CoV-2 RNA. MRI revealed signal changes in brainstem, 6th nerve nuclei, hypothalamus, thalami, mamillary bodies and medial temporal lobes. Both cases improved partially following supportive care. While ophthalmoparesis improved in 2nd patient, 1st patient continued to have diplopia at one month follow up. These cases plus a) evidence of olfactory bulb damage in form of hyposmia, b) detection of SARS-CoV-2 RNA in hypothalamic neurons on autopsy studies and c) demonstration of trans-synaptic spread of virus to limbic system following intranasal inoculation in animals, do suggest a direct role for virus in causing hypophysitis and attendant ophthalmoparesis, though it remains to be confirmed. Furthermore a role for immune mechanism/hither to unidentified metabolic insult related to virus can also not be ruled out.

Dinkin et al. [61] also reported two patients with ophthalmoparesis following SARS-Cov-2 infection. First patient presented with diplopia, left eyelid ptosis and paresthesias in both legs four days after onset of fever which resolved by the time he developed these symptoms. Examination revealed bilateral abducens palsy, left partial 3rd nerve palsy, gait ataxia and hyporeflexia in both lower limbs. MRI revealed left 3rd cranial nerve enhancement. He improved following intravenous immunoglobulin at dose of 2 g/Kg. Final diagnosis was Miller Fisher syndrome. Second patient presented with fever, cough and painless diplopia. Nasopharyngeal swab revealed SARS-CoV-2 RNA. Chest X ray was consistent with pneumonia. Bilateral optic nerve sheaths and posterior Tenon capsules showed enhancement on Gadolinium enhanced MRI. In view of optic nerve sheath enhancement, a direct viral invasion of leptomeninges was thought to be the cause of neurological syndrome, though parainfectious demyelination could not be ruled out completely.

These cases suggest a role for SARS-CoV-2 virus in ophthalmoparesis and we may see more cases as the pandemic continues to spread worldwide. These cases also stress on need to do SARS-CoV-2 RNA testing in patients presenting with ophthalmoparesis in current scenario. Future studies will help in better elucidation of role of SARS-CoV-2 in various neurological manifestations including ophthalmoparesis.

5.6. Neurocysticercosis (NCC)

Same problems plaque knowledge of the neuro-ophthalmological manifestations of NCC as is true for other infectious diseases. Despite decades of research, there are no well planned prospective series evaluating neuro-ophthalmological complications in NCC. Accordingly, most of our knowledge is derived from retrospective studies, case series and case reports.

In a landmark study, Keane JR (1982) [62] reported 56 patients with NCC and neuro-ophthalmic signs over 11 year period. Most common neuro-ophthalmic manifestation was papilledema seen in 37 (66.1%) patients. Overall six patients presented with diplopia. On examination five patients had upward gaze paresis, four had skew deviation and three had 6th cranial nerve palsy secondary to raised ICP.

NCC can cause ophthalmoparesis in several ways. It can cause several brainstem syndromes through mass effect and compression of adjacent structures. Various brainstem syndromes reported in NCC include a) bilateral eyelid ptosis due to midbrain nuclear lesion [63], b) progressive supranuclear palsy like syndrome [64], c) dorsal midbrain syndrome (upward gaze palsy, skew deviation, convergence retraction nystagmus, pupillary abnormalities) secondary to either hydrocephalus, cysts in dorsal midbrain and midbrain infarction secondary to cysticercal meningo-vasculitis [65], bilateral eyelid ptosis with MR palsy due to midbrain lesion [66], superior division of 3rd nerve palsy due to

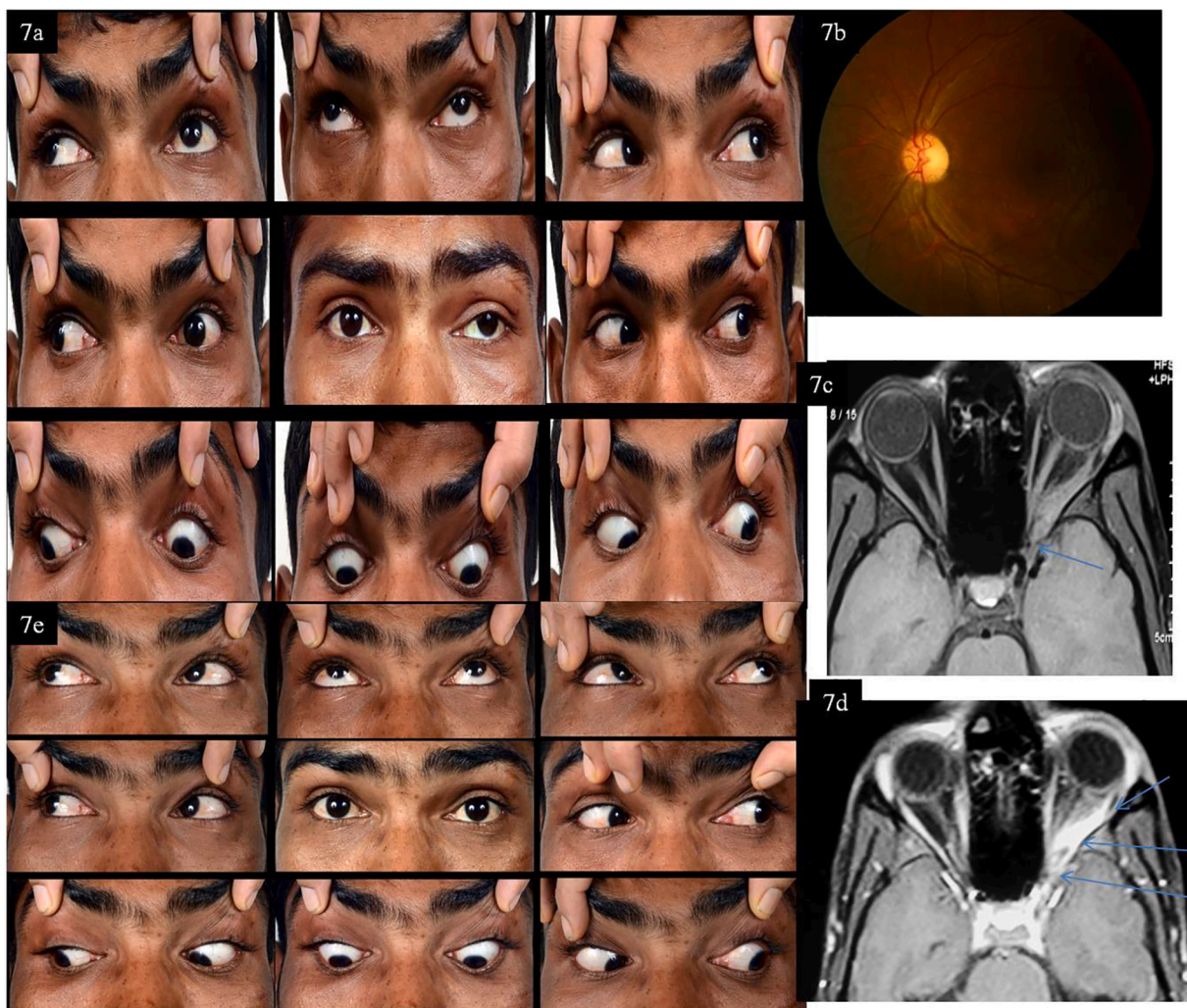


Fig. 7. Orbital apex syndrome due to neurocysticercosis. Note: Ptosis, proptosis and restriction of adduction in left eye (7a) along with optic atrophy on left side (7b); 7c and d: T1 weighted magnetic resonance images showing cyst at orbital apex along with thickened lateral rectus muscle with diffuse contrast enhancement; 7e: Complete recovery after a course of steroids and albendazole.

midbrain lesion [67], INO [68], Weber syndrome [69], pupillary sparing partial 3rd cranial nerve palsy due to midbrain lesion [70], 3rd cranial nerve palsy [71], and vertical one and a half syndrome with contralateral palsy of horizontal gaze [72]. Thus, practically every kind of midbrain syndrome can occur with NCC. In addition, NCC can present with 6th cranial nerve palsy secondary to raised ICP either due to a) multiple cysticerci with mass effect, b) obstructive hydrocephalus resulting from CSF outflow obstruction either due to i) intraventricular NCC or ii) cysticercal meningitis and adhesions in subarachnoid space [62,65]. In addition NCC can present rarely as CSS [73] or SOF or orbital apex syndrome (Fig. 7) as well [unpublished data in our institute].

5.6.1. Orbital neurocysticercosis

NCC can also affect orbital structures also. The most common sites of orbital NCC include extraocular muscles followed by subconjunctival space, adnexa, optic nerve and retro-orbital space. SR is the most common extraocular muscle involved followed by LR. Clinical features include restriction of ocular motility, proptosis, eyelid ptosis, chemosis, vision loss, pain, periorbital swelling and orbital cellulitis like picture. Cases of NCC affecting levator palpebrae superioris have also been described [74,75]. In one review on orbital NCC from Southern India ($n = 171$), most common symptoms were peri-orbital swelling, proptosis, and ptosis seen in 38%, 24% and 14% of patients respectively. Examination revealed restriction of ocular motility in 64.3%, proptosis in 44.4% and diplopia in 36.8%. Most common site of orbital NCC was extraocular muscles with SR being the commonest. 158 patients were given only medical treatment (149- oral albendazole + prednisolone; 1-oral albendazole alone; 7- oral prednisolone alone; 1- praziquantel). Out of 138 patients followed, 109 resolved nearly completely [75].

Diagnosis of NCC is based on the combination of clinical picture, epidemiological profile, serological testing for NCC and neuroimaging. Treatment includes antiparasitic treatment with or without steroids or steroids alone. Surgery is indicated for intraventricular cysts or ocular NCC. Detailed discussion about diagnosis and management of NCC is beyond the scope of this chapter and readers can refer to articles on NCC for the same.

5.7. Aspergillosis and mucormycosis

5.7.1. Cavernous sinus syndrome

The CS is part of cranial dural venous sinus system lying on both sides of sella turcica and extending from SOF anteriorly to the petrous part of temporal bone posteriorly [76]. It contains the cavernous carotid segment of the internal carotid artery (ICA) and its branches, the sympathetic plexus, the ocular motor nerves, trigeminal divisions V1 and V2, and multiple venous tributaries and spaces. The proximity to several other important structure including the paranasal sinuses makes it susceptible to multiple pathologies like infections, malignancies, A-V fistulas, aneurysms and other pathologies [77].

Nothing scares a neurologist more than the diagnosis of CSS, primarily due to the serious nature of etiologies associated with CSS and the vital structures which are contained within the CS [78]. Furthermore, anatomical complexity and presence of important structures within it, makes CS, more often than not, non amenable to biopsy. Thus, diagnosis of CSS is often based on clinico-radiological findings and treatment is often administered empirically.

In developing nations, fungal infections constitute a sizeable percentage of CSS which is defined as "involvement of at least two of the third, fourth, fifth (V1, V2) or sixth cranial nerves, or involvement of at least 1 of them in combination with a radiologically confirmed cavernous sinus lesion [24,78]. In the largest prospective series on CSS ($n = 73$) from India, fungal infections were the second commonest cause of CSS after malignancy accounting for 24.6% ($n = 18$) of all cases. Aspergillosis ($n = 12$) was the most common fungal infection followed by mucormycosis ($n = 6$). Other infectious causes for CSS were septic CS thrombosis ($n = 3$) and tuberculosis ($n = 1$) [24,78].

5.7.1.1. CS Mucormycosis. CS mucormycosis (Fig. 8) typically occurs in patients with uncontrolled diabetes mellitus, hematological malignancies with neutropenia, steroid treatment, organ transplant, chemotherapy and chronic kidney disease [79]. The main predisposing factors for mucormycosis include iron overload and deferoxamine therapy. Mucormycosis should be considered strongly in immunocompromised patients who present with CSS. In its commonest form, mucor extends into the CS or SOF by contiguous spread from adjacent nasal sinuses. Painless ulceration along with necrosis of hard palate is characteristic feature of mucormycosis [80]. Mucor has tendency to adhere to internal elastic lamina of the blood vessel causing thrombosis along with ischemia and necrosis of blood vessel wall. Thus, mucormycosis of CS may lead to cavernous sinus thrombosis [79]. Most common symptoms include headache, vomiting and eye symptoms such as proptosis, chemosis and ophthalmoplegia [80]. Other features include eschar in the nasal cavity and hard palate with multiple cranial nerve palsies and intracranial complications like epidural abscess and sagittal sinus thrombosis.

Tissue biopsy and nasal scrapping reveal mucormycosis as broad irregular, non-septate right angled hyphae invading blood vessels. NCCT (non contrast enhanced computed tomography scan) may show mucosal thickening and absence of air fluid level in infected sinuses as well as destruction of medial orbital wall with invasion of rectus muscles [81]. Gadolinium enhanced MRI of brain with CS cuts shows T1 hyperintense and T2 hypointense lesion with slow flow in ipsilateral ICA in vicinity of mucor invasion [81,82]. Diffusion weighted imaging (DWI) reveals restricted diffusion with apparent diffusion coefficient (ADC) reversal due to decreased perfusion in watershed areas resulting from narrowing of ICA in CS. This finding helps to differentiate CSS due to fungal infections from carcinoma [82].

Management of mucormycosis includes correction of predisposing factors, early treatment with conventional or liposomal Amphotericin B and surgical debridement. Therapy is given until there is evidence of complete clinical and radiological resolution. Posaconazole (15 mg/kg in split doses) can be given as salvage therapy in non-responders [83].

5.7.1.2. Aspergillosis of CS. Unlike mucormycosis which invades the CS by contiguous spread from a primary focus in the nasal sinuses or orbits, Aspergillus species can infect the CS either by contiguous spread from the adjacent nasal sinuses or by hematogenous spread. Thus, absence of sinus disease should not rule out CS aspergillosis. The clinical picture of CS Aspergillosis is almost similar to CS mucormycosis except that it is more indolent. Diagnosis of aspergillus is established on biopsy which reveals non-pigmented, narrow septate hyphae with acute angle branching at 45 degrees. Serum galactomannan has a sensitivity of 56% and specificity of 97% for diagnosis of aspergillosis [84,85]. Contrast enhanced computed tomography (CECT) scan of paranasal sinuses shows sinusitis, bone erosion and periorbital tissue destruction. On brain MRI, Aspergillus sinusitis reveals hypo/hyperintense signal changes on T1 weighted images and hypointense signal changes on T2 weighted images. This T2 shortening is due to presence of iron and magnesium (paramagnetic substances) in the lesions. The MRI characteristics of aspergillus granuloma is extremely hypo on T2 weighted and hypo- or iso- on T1 weighted imaging [84,85]. Treatment of choice is voriconazole which is given in an IV loading dose of 6 mg/kg 12 hourly for 1 day followed by oral maintenance dose of 4 mg/kg twice daily. Alternative regimens include oral loading of 400 mg twice daily for 24 h followed by 200 mg twice daily for patients weighing >40 Kg and 200 mg twice daily for 24 h followed by 100 mg twice daily for patients weighing <40 Kg [86].

5.7.1.3. Our experience of fungal CSS and recommendations. We have prospectively evaluated 50 patients (36- men, 14- women) of fungal CSS from 1st July 2018 onwards (unpublished data). 16 (32%) patients were below 40 years of age. 25 (50%) patients had definite mucormycosis and

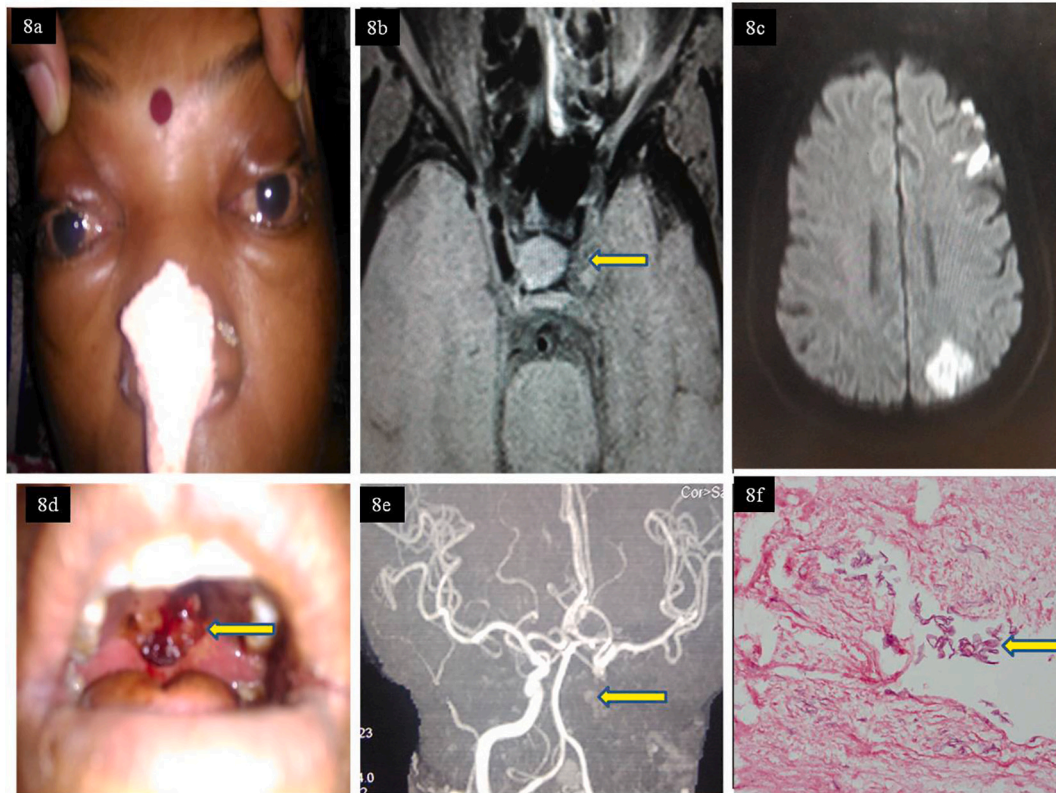


Fig. 8. Cavernous sinus mucormycosis in a young diabetic lady with bilateral ophthalmoplegia. Note: divergent squint (8a), soft tissue hyperintensity in left cavernous sinus on T1 weighted images (8b), water shed infarcts in left middle cerebral artery territory on diffusion weighted images (8c), charring of soft palate (8d), non visualization of internal carotid artery on magnetic resonance angiography (8e) and fungal hyphae on histopathology (8f).

19 (38%) patients had definite aspergillosis, based on nasal/paranasal sinus biopsy. The mean duration of illness was 55.3 ± 74.5 days. The duration of illness continue to be alarming high for a disease with lethal outcome if left alone and which can be treated with proper treatment. Most common symptoms included headache (94%), visual loss (72.9%), eyelid ptosis (66%), diplopia (78%), intra-orbital pain (78%) and facial numbness (70%). Seizures, hemiparesis and/or altered sensorium were seen in 14% of patients. 58% patients had history of diabetes which was uncontrolled in 75.8%. Constitutional symptoms such as fever and weight loss were present in <25% of patients. Meningeal signs were seen in only 6% of patients. The clinical features which favored diagnosis of mucormycosis over aspergillus included short duration of illness, duration of illness less than 7 days, presence of diabetes mellitus, poor control of diabetes, facial numbness, presence of visual loss and severe vision loss (visual acuity of 6/60 or worse). The only clinical feature which the favored diagnosis of CNS aspergillosis was a past history of CSS and presence of comorbidities other than diabetes. CT scan of the brain showed evidence of sinusitis involving at least one sinus in 98% of patients, the commonest site being sphenoid sinus. Evidence of brain infarct was seen in 15.4% of patients. A gadolinium enhanced MRI showed radiological evidence of CS lesion in 98%. One patient had evidence of orbital apex involvement on MRI with involvement of V2 division of 5th nerve suggesting CS involvement. Other common findings seen on MRI were evidence of destruction of bony wall of paranasal sinuses (74%), findings suggestive of thrombosis of internal carotid artery (ICA) (48%) and brain parenchymal spread of disease process (28%). There was a significantly higher incidence of mucormycosis of CS in patients with non visualization of ICA on MRI ($p < 0.0001$) and evidence of ethmoidal sinusitis on CT scan. The patients were treated with voriconazole in aspergillus group and amphotericin in mucormycosis group. At six month follow up, in mucormycosis group ($n = 25$), 36% improved, 36% died while 28% remained status quo. In aspergillus

group ($n = 20$), 75% had improved while 25% had remained status quo. In our previous published data [24], we have found clinical evidence of severe visual loss, nasal blockage and presence of diabetes to favor diagnosis of fungal CSS compared to other etiologies, while bilateral CSS suggested diagnosis other than fungal CSS. Radiological features suggestive of fungal CSS included evidence of bone erosion ($P = 0.0001$), paranasal sinus disease ($P = 0.0001$) and narrowing of ICA ($P = 0.0001$).

Based on our experience and previously published data, we suggest that diagnosis of fungal CSS can be made with certainty in most of the cases based on clinico-radiological picture alone. It is also possible to judge the nature of causative fungus and predict prognosis based on clinical and radiological features. Thus, in suspected case of fungal CSS, it seems reasonable to start empirical antifungal treatment while waiting for more definite results. The good outcome can be achieved in close to 60–70% of patients with proper treatment.

Other infectious causes of CSS include TB, NCC, viruses like VZV, syphilitic gummas and other rare fungi. Their diagnosis and management has been discussed already.

5.7.2. CNS fungal infections

Rarely fungal infections other than cryptococcosis may cause meningoencephalitis with brainstem infarcts or brainstem granulomas with attendant ophthalmological signs of brainstem involvement. In most cases, diagnosis can be made by the clinical profile, neuroimaging and CSF findings.

5.8. Septic cavernous sinus thrombosis

Among all the CSS, nothing is more dramatic than septic CS thrombosis (CST). Septic CST results from combination of infection and thrombosis within CS. CS receives blood from face via superior and inferior ophthalmic veins and from sphenoidal and middle cerebral

veins. It drains into superior and inferior petrosal sinuses. Most common cause of spread of infection to CS is sinusitis. However connecting veins do allow infections of medial side of face, nose, teeth, tonsils, orbit and palate to spread to CS resulting in septic CSS. Causative organism is *Staphylococcus aureus* in approximately 70% of cases [87,88]. Other organisms include streptococcus, gram negative bacilli and anaerobes. The clinical picture is dramatic with high grade fever, severe often excruciating headache (usually in distribution of 1st and 2nd division of 5th cranial nerve), orbital pain, peri-orbital swelling and visual impairment. Examination reveals conjunctival injection, proptosis, periorbital edema, ptosis, palsies of 3rd, 4th and 6th cranial nerves with hypoesthesia in distribution of 1st and 2nd divisions of 5th nerve. Raised intraocular pressure may be reflected in decreased visual acuity and optic disc swelling. Visual loss may also result from traction on the optic nerve and vascular disease of the central retinal artery or ICA. Septic CST may become bilateral and appearance of signs and symptoms in other eye is considered highly suggestive of CST. Diagnostic work up includes routine testing with blood cultures. Diagnosis may be confirmed by CECT of CS region or by GdMRI of brain including CS. Treatment includes administration of antibiotics along with supportive care. Empiric choice of antibiotics should include coverage against methicillin resistant *Staphylococcus aureus* pending results of culture sensitivity [89].

5.9. Lyme disease

Lyme disease, caused by spirochete *Borrelia burgdorferi*, results from exposure of humans to Ixodes tick vector. The disease is common in United States (especially along the Northeastern seaboard, the upper midwest, and, to a much lesser extent, the west coast), Scandinavian countries and central Europe during spring through fall. The disease evolves in three stages named early localized, early disseminated and late disease. Early localized phase appears within 3–30 days of tick bite and is characterized by erythema migrans. It may be associated with systemic symptoms such as fever, headache, malaise, lymphadenopathy, muscle and joint pains, etc. Early disseminated disease appears 3–5 weeks after tick bite and consists of multiple erythema migrans, cranial nerve palsies (especially facial palsy which may be bilateral), meningitis, systemic symptoms (fever, headache, weakness, neck stiffness and lymphadenitis) and carditis. A painful radiculoneuritis (Bannwarth's syndrome) is especially common in Europe. Late manifestations appear weeks to months after tick bite and include arthritis (most common), encephalitis, encephalopathy, peripheral neuropathy and acrodermatitis chronica atrophicans (especially in Europe). Cranial neuropathies related to Lyme disease typically occur during early disseminated phase and most commonly affect facial nerves [90]. However cranial neuropathy may involve any of ocular motor nerves unilaterally or bilaterally. Ocular motor palsies may rarely be presenting feature of Lyme disease also [91–94]. Keys to diagnosis include a) recognition of ocular motor palsy as a rare presenting feature of Lyme disease especially in endemic regions, b) appropriate diagnostic tests and c) careful history of other manifestations including erythema migrans. In isolated meningitis or radiculitis without rash, CSF may show lymphocytic pleocytosis and raised protein but culture is rarely positive. Diagnosis in isolated cranial neuropathy rests on demonstration of IgM anti *Borrelia* antibodies [90]. While oral treatment with doxycycline or amoxicillin for 10 days may suffice for isolated cranial neuropathy, intravenous treatment with ceftriaxone is recommended for Lyme meningitis [90]. Overall prognosis for recovery with appropriate treatment is excellent.

5.10. Skull base osteomyelitis (SBO)

SBO is potentially life threatening condition most commonly resulting from ill treated persistent otitis externa (malignant otitis externa) in immunocompromised or diabetic elderly people. SBO secondary to malignant otitis externa involves temporal bone and commonly affects 7th cranial nerve plus lower cranial nerves. Ocular

motor nerves are involved only rarely. However SBO may occur in absence of history of malignant otitis externa. This central SBO affects sphenoid and occipital bones and is often centered on clivus. It affects abducens nerve which lies in close contact with sphenoid bone as well as other lower cranial nerves. Common clinical features of central or atypical SBO include headache, fever and symptoms referable to individual cranial nerves. A combination of 6th, 9th, 10th and 11th cranial palsies should arouse suspicion of clival pathology [95,96]. 3rd and 4th cranial nerve palsies have been reported with SBO, though rarely. Most common causative organism is pseudomonas, though SBO can also occur due to aspergillus, gram positive organisms and MTB. Diagnosis of SBO rests on documentation of otitis externa either through history or clinical examination or by appropriate investigations. Skull base CT or MRI often shows evidence of osteomyelitis along with clival enhancement. The main differential is malignancy and many a times, clival biopsy is needed to settle the issue especially in cases without any evidence of otitis externa. Treatment includes antibiotics.

5.11. Miscellaneous

Ophthalmoplegia has been reported in association with several other infections. Kim et al. [97] reported a case of CSS in scrub typhus with evidence of focal nodular lesion in the anterior CS. CSS resolved completely following treatment of scrub typhus. In addition, ocular motor palsies have been described in patients with chickungunya [98], typhoid [99], dengue [100] and leptospira [101]. In most cases diagnosis could be made through associated clinical features of the primary disease.

6. Conclusion

Infections continue to be important cause of ophthalmoplegia in the developing world. An ideal approach to infectious ophthalmoplegias is to first localize the site of disease as different infectious etiologies can be separated anatomically. Knowledge of common infectious etiologies for ophthalmoplegia and their clinical patterns is a must for an early diagnosis and appropriate treatment. Every attempt should be made to identify the causative pathogen as results can be highly rewarding with appropriate treatment.

Author contribution

1. Rajeev Ranjan: Writing -original draft writing
2. Deependra Singh: Writing - review and editing
3. Karthik Vinay Mahesh: Data curation
4. Aastha Kapila Takkar: Data curation
5. Sucharita Ray: Formal analysis, Validation
6. Vivek Lal: Conceptualization, Supervision ,Validation, Writing - review and editing

Declaration of Competing Interest

Authors declare they do not have any conflict of interest.

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