# Literature Review

## Neuro-opthalmological aspect of ocular motor abnormalities

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*The paper presents anatomical features of ocular motor nerves (cranial nerves III, IV, and VI). Vascular abnormalities are major causes of ocular motor abnormalities and include microvascular lesions, aneurysms of brain vessels, a pathology in the vertebrobasilar territory, brain neoplasms (particularly, those of the cerebellopontine angle, skull base and pituitary gland), and head trauma. Inflammation, myasthenia, endocrine ophthalmopathy, and demyelination are minor causes of ocular motor abnormalities. Ocular motor abnormalities should be differentiated from ocular motor lesions at the level of the medial longitudinal bundle such as internuclear ophthalmoplegia.*

Ocular motor abnormalities are a multidisciplinary problem that occurs in diseases of the central nervous system (brain neoplasms and vascular, inflammatory, or demyelinating diseases) or disorders of the peripheral visual system. The ocular motor system has an intricate structure and consists of ocular motor extraocular muscles; ocular motor nerves (cranial nerves (CN) III, IV and VI); ocular motor nuclei; internuclear connections; supranuclear structures and cortical centers. Since there is a close anatomic relationship between the ocular motor system and structures of the brain, the involvement in the pathological process can occur at any level of the system.

Ocular motor abnormalities in general can be divided into those of neurogenic origin and those of myogenic origin. Those of neurogenic origin are characterized by isolated or combined lesions of CN III, IV, and VI, whereas those of myogenic origin develop as a result of the primary neurogenic lesions of extraocular muscles in ocular trauma, orbital inflammation, endocrine or autoimmune disorders [1, 2].

Strabismus is an important manifestation of an ocular motor abnormality. Comitant strabismus is strabismus with full ocular motility and without ocular motor muscle paralysis or diplopia. Paralytic strabismus is caused by palsy of CN III, CN IV and/or CN VI or damage to certain muscles innervated by these nerves. Binocular diplopia is present. Paralytic strabismus may be accompanied by dizziness, nausea, disorientation, and cosmetic defects (esotropia or exotropia, absence of ocular motility, eyelid descent and wide pupils) [3].

Ocular motor nerves have an intricate structure and originate in the structures of the brain and reach the orbit as well as the globe. Thus, the ocular motor nerve (CN III) arises from two nuclei in the ventral cerebral peduncles and exits the brainstem from the interpeduncular fossa of the midbrain, passes through the cavernous sinus, enters the orbit through the superior orbital fissure and innervates the ocular motor muscles and the ciliary ganglion [4]. The trochlear nerve (CN IV) originates from the trochlar nuclei in the midbrain, exits at the dorsal side of the midbrain, enters the orbit through the superior orbital fissure and innervates only the superior oblique muscle. The abducens nerve (CN VI) arises from the pons on the floor of the rhomboid fossa, and exits the cranial vault via the superior orbital fissure to enter the orbit and innervate the lateral rectus muscle [4, 5].

Ocular motor abnormalities may be the manifestations of a neurosurgical disease (brain neoplasms, brain aneurysms, or head trauma). Because it is ophthalmologists whom patients see for their ocular symptoms, they should be on the alert for the symptoms of a neurosurgical disease, and if a patient has these symptoms, s/he should be promptly referred to the allied health professional(s).

Ocular motor nerve palsy can be manifested by (1) a limited ability to rotate the eye upward, downward, or inward, (2) mydriasis, (3) ptosis, (4) exotropia because of the still functioning lateral rectus muscle; and (5) horizontal and vertical diplopia. Abducens nerve palsy can be accompanied by esotropia, paresis of outward movements of the eye, and a horizontal diplopia which is maximal on looking towards the affected side. The trochlear nerve innervates only the superior oblique muscle that rotates the eye downward and inward. This is rarely individually involved in the pathological process. In trochlear nerve damage, there is esotropia and diplopia on looking downwards (the patient cannot go down the stairs) [3].

Vascular brain pathology is a major cause of ocular motor abnormalities, with more than 40% of patients with an ocular motor abnormality having vascular lesions (a pathology in the territory of the internal carotid artery, including aneurysms of the supraclinoid portion or the infraclinoid portion, in 67% of patients, and a pathology in the vertebrobasilar territory in 32% of patients) [1, 6]. Massive brain tumors such as neoplasms of the cerebellopontine angle, skull base and pituitary gland also may result in ocular motor nerve compression (37%) [1]. In addition, severe head trauma causes ocular motor abnormalities in 20.1% of patients, and inflammatory processes (Tolosa Hunt syndrome or giant cell arteritis) in 2.6% of patients, although the authors vary in the causes suggested for the development of ocular motor abnormalities [6, 7].

Fang and colleagues [8] found that the most common causes of acquired third nerve palsy were presumed microvascular (42%). Microvascular ischemia may cause ocular motor nerve palsies. A patient with microvascular ischemia and ocular motor nerve palsy may have at least one risk factor (including diabetes, hypertension, hypercholesterolemia, coronary artery disease, myocardial infarction, stroke and tobacco use) for ischemia. Patients who are suspected for ischemia require neuroimaging studies to exclude neurosurgical pathology. The diagnosis is made when there is no MRI evidence of pathological changes or other causes of ocular motor abnormalities [9, 10]. Given the presence of a number of risk factors, patients with isolated third, fourth or sixth cranial nerve palsies are at high risk for the development of ischemic stroke [11].

Head trauma may cause the development of ocular motor abnormality. A severe head trauma with loss of consciousness, skull base fractures, and subarachnoid hemorrhage is a more common cause of ocular motor abnormality than a mild head trauma [12]. Ocular motor nerve palsy may occur in patients with subdural hematoma. Traumatic impact may be direct or indirect (in case of increased intracranial pressure) and occur at any location of the nerve – from brainstem nuclei to the extraocular muscle. The major mechanisms of this nerve damage include nerve compression, strain, rupture or infiltration of the ocular motor nerves [13].

Sometimes ocular motor nerve damage is not permanent but transitory and presents itself in the form of transitory attacks. Transitory ocular motor nerve palsies occur in the presence of parasellar tumors, painful ophthalmoplegia, cavernous aneurysms, idiopathic intracranial hypertension, primary systemic sclerosis, sphenoiditis, and skull base tumors. In addition, transitory ocular motor nerve palsies may be idiopathic [3, 5]. Idiopathic ocular motor nerve palsy is a diagnosis of inclusion in the absence of intracranial damage, traumatic lesions, inflammation or microischemia. Hormonal therapy (prednisolone orally) for two weeks is recommended for these cases. Although ocular motor function recovery may occur fast, cases with no improvement have been reported [6, 14, 15,].

One or more ocular motor nerves may be involved in the pathological process. The involvement of two or more ocular motor nerves is more common for a cavernous sinus disease (brain neoplasms, vascular aneurysms, or carotid cavernous fistula) in which these nerves are located closely to each other. Occasionally, total ophthalmoplegia may occur, which manifests itself as total ptosis, mydriasis and total loss of ocular motility [16].

The most common cause of third cranial nerve palsy was presumed inflammatory lesions [17]. Risk factors associated with ischemic third cranial nerve palsy are age older than 65 years, hypertension, coronary artery disease, and smoking. Mydriasis is not common in patients with this type of palsy. Isolated ocular motor nerve palsies require taking several factors into consideration including age, whether and which comorbidities are present, patient's disease history, etc [18].

Fang and colleagues [8] aimed to determine the incidence and etiologies of acquired third nerve palsy, and found that while compressive lesions had a higher likelihood of pupil involvement, pupil involvement did not exclude microvascular third nerve palsy and lack of pupil involvement did not rule out compressive third nerve palsy. These patients should have prompt neuroimaging (brain MRI or CT). Because a tumor may also compress superficial pupillary fibers, neuroimaging is a must in any case of diplopia in the presence of pupillary changes.

All patients with isolated ischemic ocular motor nerve palsy complain of diplopia which may develop suddenly [19]. Some patients may exhibit periorbital pain, and those with third cranial nerve palsy may have ptosis. Anisocoria is more common in aneurysms, Tolosa Hunt syndrome, meningioma, leptomeningeal carcinomatosis, lymphoma, and herpetic lesions [10, 11, 17, 20].

Ocular motor nerve palsy may be congenital, sometimes associated with amblyopia and not with pain [21].

Ocular motor nerve palsy is uncommon in B-cell lymphoma at the level of ocular motor nerve nuclei, cavernous sinus or superior orbital fissure [22].

Patients with cryptococcal meningitis and increased intracranial pressure may experience ocular motor nerve palsies due to inflammation in the nerve [23].

Major causes of sixth nerve palsy are trauma, inflammation, neoplasm, vascular lesions and idiopathic. Minor causes are myasthenia, endocrine ophthalmopathy, orbital metastases, and demyelination [24, 25].

Jung and colleagues [20] reported that the most common etiologies of fourth cranial nerve palsy were vascular (51.3%), congenital (20.0%), and idiopathic (18.5%).

It has been suggested that a certain proportion of ocular motor abnormalities previously considered to be idiopathic may be due to ocular motor nerve lesions of viral origin (herpes simplex viruses type 1 and type 2 (HSV1 and HSV2); varicella-zoster virus (VZV); and human herpes viruses types 6, 7, and 8 (HHV6, HHV7, and HHV8)). It has been demonstrated that viruses can spread through the trigeminal, abducens, ocular motor, and facial nerves, causing ocular motor abnormalities of various severity [26]. The major complaints are diplopia (94.3%), esotropia (65.7%), exotropia (22.95%), and ptosis (17.1%) [27].

Patients with carotid-cavernous fistula (CCF) have special neuro-ophthalmological symptoms. This condition is caused by an arteriovenous fistula in the cavernous sinus, which represents an abnormal shunt between the internal carotid artery and the venous sinus. Its major etiologies are head trauma and spontaneous in patients with systemic vascular disorders such as hypertension, atherosclerosis, and etc. [19]. The typical features are a loud pulse-synchronous bruit audible to the patient and also audible on auscultation over the eye; exophthalmos; hyperemic conjunctival vessels; eyelid edema and conjunctival chemosis; globe pulsation; poor ocular motor functions due to the effect on the ocular motor nerves (in the cavernous sinus) and the extraocular muscles; and elevated intraocular pressure due to increased pressure in the episcleral veins. Fundus vessels usually appear hyperemic, with tortuous retinal veins and narrowed retinal arteries, but optic disc edema caused by reduced venous outflow from the orbit is less common. Hemorrhage along the course of blood vessels may occur [28, 29]. Patients with spontaneous CCF have clinically less apparent symptoms, which may cause difficulties in the diagnosis. Carotid angiography and brain MRI and CT are required for diagnostic evaluation [1].

Since ocular motor abnormalities are commonly accompanied by diplopia and significantly impair quality of life, ocular motor function recovery is essential. The ocular motor function recovery rate has been reported to be higher for patients with microischemic lesions in the presence of diabetes mellitus (71.9%) than for patients with intracranial aneurysms (36%) [30].

Ocular motor abnormalities should be differentiated from ocular motor lesions at the level of the medial longitudinal bundle (MLB) in the brainstem, such as internuclear ophthalmoplegia. The MLB connects the 3rd nerve nucleus on one side to the 6th nerve nucleus on the opposite side of the brain stem, and provides for conjugate horizontal and vertical gaze [3, 5]. The neuro-ophthalmological symptoms are poor adduction, oblique deviation, and impaired conjugate gaze.

Underlying causes of internuclear ophthalmoplegia include multiple sclerosis, brain stem infarction or tumor, brainstem encephalitis, meningitis, metabolic encephalopathy, systemic lupus erythematosus, head trauma, Arnold-Chiari malformation, vascular aneurysms, ophthalmoplegia migraine, and cavernous sinus thrombosis [5].

Early diagnostic evaluation of ocular motor abnormalities and referral to the allied health professional(s) are essential for detecting challenging neurological and neurosurgical conditions and providing prompt health care to patients.

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