

# Clinical Evaluation, Prevalence and Etiologic Factors in Patients with Ophthalmoplegia

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## Abstract

**Purpose:** Ophthalmoplegia makes many physicians to refer the patients to neurologists and/or ophthalmologists for neuro-ophthalmic evaluation. Ophthalmoplegia has different etiologies some of which may be very harmful and need urgent intervention. Prevalence of the disease is not obvious. This study is designed to evaluate the various etiologies and their prevalence in this disorder.

**Methods:** This descriptive case series study was conducted on 226 patients with ophthalmoplegia referred to adult neurology clinic between the years 2005 to 2009. An informed consent was taken, considering inclusion and exclusion criteria. All patients had a complete neurologic and ophthalmologic examination. Case based laboratory and imaging techniques were used to determine the etiology of the ophthalmoplegia. Data were analyzed by  $\chi^2$  test.  $P < 0.05$  was considered significant.

**Results:** Totally 226 patients were enrolled, including 121 (53.5%) males and 105 (46.5%) females ( $P > 0.05$ ). The age range was between 19-72 years (mean  $56.2 \pm 11.2$ ). Symptoms were unilateral in 215 (95%) patients. Most common etiologies were diabetes mellitus (16.8%), infectious disorders (14.6%), intracranial tumors (13.2%) and head trauma (11.1%). Other common etiologies were orbital tumors (7.1%), posterior communicating artery (PCA) aneurysm (5.3%), and orbital pseudo tumors (4.0%). The etiologic factors were not identified in 4% of cases.

**Conclusion:** Ophthalmoplegia has many different etiologies some of which such as aneurysms can be potentially very dangerous and need careful and urgent management, while some others can be easily treated. Management is very important and warrants the cooperation and intervention of ophthalmologists and neurologists simultaneously.

**Keywords:** Ophthalmoplegia, Painful Ophthalmoplegia, Pain, Ocular Nerves

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## Introduction

The entity of ophthalmoplegia may be painful or painless. In the painful unilateral ophthalmoplegia the pain may be focused in or around the orbit that is accompanied with ipsilateral ocular motor paresis. Sometimes Horner syndrome and sensory loss in the ophthalmic division of the 5<sup>th</sup> cranial nerve are added to the symptoms.<sup>1,2</sup> The pain if present, usually disturb and limit the patient's activities and is an important complaint in the emergency ward or neurologist/ophthalmologist office.<sup>2</sup> There are many etiologies with different categories, such as vascular [aneurysm, diabetes, migraine, temporal arteritis (TA)],<sup>3-7</sup> neoplastic (pituitary adenoma, metastasis to dura, nasopharyngeal tumor),<sup>8-11</sup> inflammatory and infectious disorders [Tolosa Hunt syndrome (THS), orbital pseudotumor, sarcoidosis, systemic lupus erythematosus (SLE), Wegner] and cranial trauma.<sup>12-18</sup> In a majority of cases diabetes mellitus is either the main etiology<sup>19-21</sup> or may be present as a risk factor in many other cases, such as mucormycosis and herpes zoster.<sup>22,23</sup> The basic mechanism of ophthalmoplegia in diabetes is vascular infarct of the vasa nervorum as a presentation of diabetic mono-neuropathy.<sup>24</sup> Previous studies have confirmed ischemic infarct of nerve as a consequence of disturbances in microcirculation contributed to the cause of diabetic ophthalmoplegia.<sup>25,26</sup> Among other prevalent causes of ophthalmoplegia, the most painful ones are tumors and malignancies. Most of these tumors are around the cavernous sinus on the lateral sides of the sphenoid bone, from the superior orbital fissure to the apex of the petrous temporal bone. Internal carotid artery, abducent, oculomotor, trochlear and ophthalmic and maxillary division of trigeminal nerves are usually in the thickness of the lateral wall of the sinus. Compact and delicate anatomical structures in and around the cavernous sinus describes why tumors and other pathologic lesions in this region can cause ophthalmoplegia. Pain, if present, is due to the pressure or stretching effects of the tumors on trigeminal nerve, vascular structures, and dura especially in skull base. Ophthalmoplegia is mainly an effect of direct invasions or pressure on ophthalmic nerves.<sup>27</sup> Although there are many etiologies for this

disorder some etiologies are very rare and some others are more prevalent. Incidences of these disorders are not clear and there are no sufficient statistical information about this problem especially in none developed countries. This study is designed to evaluate the etiologies of this disorder for better approach in such patients.

## Methods

This descriptive case series study was conducted on 226 patients with ophthalmoplegia. They were referred to adult neurology clinic or ophthalmology clinic for evaluation and management of ophthalmoplegia from 2005 to 2009. All referred patients were above 19-year-old. The study protocol was based on the tenets of the Declaration of Helsinki and approved by the institutional review board and ethics committee of Shahed University. After taking an informed consent, clinical examinations were made by neurologist and ophthalmologist. Laboratory and imaging such as brain and orbital computerized tomography scans (CTs) or magnetic resonance imagings (MRI) were requested according to the results of the clinical examination and localization of the lesion or pathologic process. Fasting blood glucose (FBS), complete blood count (CBC) and erythrocyte sedimentation rate (ESR) tests were assessed in all patients and history of hypertension and cigarette smoking were recorded. A detailed history including, onset, duration, timing, frequency, quality and severity of pain were recorded for all patients. Thorough ophthalmologic and neurologic examination with focus on eye movement and head and neck posture were performed. All new onset or histories of ophthalmoplegia for less than 6 months were included. Patients with any past history of cerebrovascular accident (CVA), parkinson diseases or parkinsonism syndromes, myasthenia gravis and chronic multiple sclerosis with any systemic manifestations or any other definite neurologic or ophthalmologic disorders such as thyroid related orbitopathy, restrictive orbital fractures, progressive external ophthalmoplegia, and Brown or Duane's syndromes, were not permitted to enter the study. Forced duction and forced generation tests were used to discriminate between

paralytic or restrictive ophthalmoplegia in orbital fracture cases. Hypertension, alone, was not considered as an independent etiologic factor. According to the patient's possible diagnosis, all through needed para-clinical tests and imaging were requested and the additional or non-related tests were avoided. Data were analyzed by  $\chi^2$  test and  $P < 0.05$  was considered significant.

## Results

Totally 226 patients were included in this study for evaluation of ophthalmoplegia during a five-year's period from 2005 to 2009. We excluded 36 patients in those, 15 patients were missed during the follow-up study, 10 had chronic multiple sclerosis with systemic manifestations, 6 had systemic myasthenia gravis and 5 had CVA. Finally 226 patients completed the follow-up study in which 121 (53.5%) were male and 105 (46.5%) were female (Table 1). Statistical analysis showed no significant difference regarding the sex factor ( $P > 0.05$ ). The mean age range of the patients was  $56.2 \pm 11.2$  (19-72) years. About 146 (64.5%) patients were older than 50 years. Symptoms were unilateral in 215 (95%) patients. Right and left eyes were involved in 111 (49%) and 104 (46%) patients respectively. In 11 (5%) cases, symptoms were bilateral simultaneously or manifested recently. There was no significant difference in the laterality of ocular involvement ( $P > 0.05$ ). Diabetes mellitus was present in 76 (33.6%) patients, and hypertension was present in 52 (23 %) patients, 29 (13%) patients were already smokers and 20 (9%) patients had the history of smoking for at least one year. The mean duration of the symptoms was  $96 \pm 12$  (7-150) days. Corrected visual acuities (VAs) in affected eyes were  $20/40$  (logMar 0.30) or better in 172 (76.1%) cases and were lower

than  $20/40$  in 54 (23.9%) cases. Visual field (VF) defects, mostly unilateral were present in 16% of the affected cases. Types of VF defects differed depending on the etiologic factors. Diabetic neuropathy was the most prevalent risk factor for ophthalmoplegia and was present in 38 (16.8%) patients. The 3<sup>rd</sup>, 6<sup>th</sup> and 4<sup>th</sup> cranial nerves paresis were the most common nerves involved in diabetic patients (56%, 40% and 4% respectively). The other most prevalent etiologies were infectious disorders that were present in 33 (14.6%) patients and the leading agent in this category was herpes zoster in 18 (8.0%) cases. The following most prevalent etiologies were intracranial tumors that in overall, 30 (13.2%) cases were involved. Among these, peri-cavernous sinus meningioma and pituitary adenoma together were more prevalent and were present in 17 (7.4%) cases. The other common cause was traumatic ophthalmoplegia which was present in 25 (11.1%) cases. In this group the most common affected cranial nerves were 6<sup>th</sup>, 3<sup>rd</sup>, and 4<sup>th</sup> nerves (54%, 40% and 6% respectively) that were involved especially in skull base, orbit and cavernous sinus fractures. Generally in all of the cases, 6<sup>th</sup> cranial nerve was the most common involved nerve and prevalence of the 3<sup>rd</sup> and 4<sup>th</sup> nerves palsy were in second and third orders (59.5%, 42.5% and 8% respectively).

Among the laboratory tests, CBC test was within normal limit in 188 (83%) patients. Mild anemia was present in 28 (12%) and elevated white blood cells counting (WBC) was present in 38 (17%) patients. ESR was significantly elevated in all cases of TA, but mild to moderate elevations were observed in 28 (12%) patients with other etiologies. Details of etiologic factors are shown in table 2.

**Table 1.** Demographic characteristics of patients with ophthalmoplegia

| Sex    | No  | %    | Age   | Mean  | SD    |
|--------|-----|------|-------|-------|-------|
| Male   | 121 | 53.5 | 20-72 | 57.01 | 11.93 |
| Female | 105 | 46.5 | 19-70 | 55.78 | 10.07 |
| Total  | 226 | 100  | 19-72 | 56.2  | 11.2  |

No: Numbers  
SD: Standard deviation

**Table 2.** Differential diagnosis of ophthalmoplegia

| Frequent causes            | Numbers (%) | Rare causes               | Numbers (%) |
|----------------------------|-------------|---------------------------|-------------|
| Diabetes mellitus          | 38 (16.8% ) | Orbital tumors            | 16 (7.1%)   |
| Infectious disorders       | 33 (14.6%)  | PCA aneurysm              | 12 (5.3%)   |
| Herpes zoster              | 18 (8.0%)   | Orbital pseudotumor       | 9 (4.0%)    |
| Cavernous sinus thrombosis | 7 (3.0%)    | Unknown etiology          | 9 (4.0%)    |
| Mucormycosis               | 3 (1.3%)    | Carotid aneurysm          | 8 (3.5%)    |
| Sinusitis                  | 3 (1.3%)    | Migraine                  | 8 (3.5%)    |
| Orbital cellulitis         | 2 (1.0%)    | Temporal arteritis        | 7 (3.1%)    |
|                            |             | Multiple sclerosis        | 7 (3.1%)    |
| Intracranial tumors        | 30 (13.2%)  | Tolosa-Hunt syndrome      | 6 (2.7%)    |
| Miscellaneous              | 12 (5.3%)   | Nasopharyngeal tumors     | 6 (2.7%)    |
| Meningioma                 | 10 (4.4%)   | Ocular myasthenia         | 4 (1.8%)    |
| Hypophysis adenoma         | 7 (3.0%)    | Mucocele                  | 2 (0.9%)    |
| Hypophysis apoplexia       | 1 (0.5%)    | Lupus and Wegner          | 2 (0.9%)    |
|                            |             | Carotid dissection        | 2 (0.9%)    |
|                            |             | Sarcoidosis               | 1 (0.4%)    |
| Head trauma                | 25 (11.1%)  | Carotid cavernous fistula | 1 (0.4%)    |
| Total                      | 126 (55.7%) | Total                     | 100 (44.3%) |

PCA: Posterior communicating artery

## Discussion

Ophthalmoplegia may be isolated or represents as a symptom of a systemic disorder. In each case, diagnosis is based on complete case specific evaluation of the patients for various etiologies. Findings of this study showed that diabetic neuropathy is the most prevalent cause of ophthalmoplegia followed by infectious disorders, intracranial tumors and head trauma.

Diabetes mellitus has previously reported as an important cause of ophthalmoplegia by Gladstone (2004, 2007) and Greco (2009) which is similar to the results of this study.<sup>1,17,19</sup>

Infectious diseases including, herpes zoster, cavernous sinus thrombosis, mucormycosis, sinusitis and orbital cellulitis, with a prevalence of 14.6% were the second most important etiologic factors. Some infections such as herpes zoster directly affect the nerves while some others cause ophthalmoplegia with indirect mechanisms. This finding is in parallel with the studies of Gladstone and warns and others about potentially threatening causes of ophthalmoplegia especially in the painful types.<sup>1,17,23,31-33</sup>

The third most prevalent causes of ophthalmoplegia, were intracranial tumors and malignancies. The most common of these tumors were meningioma and hypophyseal adenoma. In addition to these tumors, Gladstone in two separate studies reported craniopharyngioma and chordoma as prevalent intracranial tumors, but there were no such cases in this study.<sup>1,17</sup>

Skull trauma and skull base or orbital fractures may cause ophthalmoplegia directly or indirectly via increased intra cranial pressure (ICP). In this study 25 (11.1%) patients were referred with head trauma as an etiology for ophthalmoplegia and the 6<sup>th</sup> cranial nerve was the most common involved nerve. This is similar to the studies of La Mantia and Dhaliwal and others<sup>2,28-30</sup> these results however didn't support Gladstone results in which trauma was not a major etiologic factor.<sup>1,17</sup>

Vascular origin disorders such as, posterior communicating artery (PCA) aneurysms, migraine, TA, carotid dissection and carotid cavernous sinus fistula (CCF) have different but somewhat similar mechanisms that act by direct invasion or compression of the nerves. The pain mechanisms in these cases include compression of trigeminal nerves, stretches on vessel walls and blood leakage to the subarachnoid space, but ocular symptoms are due to the direct compression of the nerves. In migraine and TA, pain and ophthalmoplegia are mainly due to ischemic process. TA is a vasculitis that affects medium and large size arteries.<sup>34</sup> The main symptoms are headache and visual loss, but occasionally ophthalmoplegia are present due to ischemia of oculomotor nerves in about 6% of cases in some reports.<sup>35</sup> Migraine with ophthalmoplegia occurs mainly in adolescents and has a vascular origin although new studies suggest that it is due to the recurrent demyelination neuropathy of ophthalmic nerves. In this study ophthalmoplegic migraine probably shows lower prevalence, because the subjects were all selected among the adult population.<sup>36-39</sup> The results of this study are similar to Gladstone and La Mantia in relation with the vascular disorders.<sup>1,2,17</sup> THS as a recurrent granulomatous inflammation in the cavernous

sinus and superior orbital fissure is another well known cause of painful ophthalmologia observed in all countries. There were 6 (2.7%) cases of THS in this study. Orbital pseudotumor is an inflammatory process that involves extra ocular muscles, sclera, lacrimal glands and may cause uveitis. THS and orbital pseudo tumor are rare conditions, diagnosed by the exclusion of the other reasons, and their prevalence is not clear in most studies.<sup>40,41</sup> In this study the prevalence of these two disorders were 6.6%.

As described above, ophthalmoplegia especially the painful type has different etiologies from diverse groups of diseases with dissimilar mechanisms and pathogenesis, a clinical entity that requires a precise investigation in each case.

## Conclusion

Ophthalmoplegia is always an obscure problem for ophthalmologists and neurologists. Etiologic and pathophysiologic diversity of this entity requires careful evaluation and investigation with close cooperation of both ophthalmologists and neurologists who are familiar with the management of these disorders. The review of the literature showed that there is not enough information about the overall prevalence or individual etiologies of this disorder. Some etiologies such as aneurysms and TA can lead to dangerous complications if left untreated or undiagnosed, but some others such as THS or orbital pseudo tumor are not much dangerous and may be treated easily. We suggest that the patients are best to refer to the compatible centers for a better management, follow-up and accurate collection of statistical information.

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