Literature Review

Differential diagnosis of patients presenting with ocular and periorbital pain: a multidisciplinary approach

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Ophthalmalgia (eye pain) is of interest to various fields of medicine, and may be due to ocular or extra-ocular causes. Common ocular causes include glaucoma, ocular inflammatory disease (like keratitis, skleritis or neuritis), and orbital disease. Notable extra-ocular causes include trigeminal neuralgia, headaches of various types, intracranial vascular lesions, and otolaryngological inflammatory disorders. The diagnosis and management of patients with ophthalmalgia requires a multidisciplinary approach with contributions from ophthalmology, neurology, neurosurgery, oto(rhino)neurology, as well as other specialties.

Keywords:
eye pain, causes, multidisciplinary approach

[There is] no general theory about pain.
Each patient discovers his own.
Alphonse Daudet

Ophthalmalgia (eye pain) is a multidisciplinary issue that is of interest not only to ophthalmology, but also to neurology, neurosurgery, endocrinology, and psychology. The eye is highly pain sensitive since it is extremely important for the human being. In addition, it must be saved to the maximal extent since approximately 90 percent of an individual's information is obtained through vision.

The cornea and ciliary processes are the main structures responsible for pain sensation in the eye. The former is the most sensitive tissue in the body, its nerve terminal density being 500 times that of the skin. The ophthalmic nerve (the first branch of the trigeminal nerve) innervates the cornea and mediates the corneal reflex. When the cornea with normal sensitivity is touched, even lightly, the pain signal is generated, and immediate response to the pain stimulus is initiated. However, the limbal cornea is substantially less sensitive than the central cornea. The cornea is extremely sensitive to mechanical influence, even to slightest epithelial damage that causes acute stabbing pain [1].

Ciliary processes also have pain receptors. Ciliary nerves originate in the first division of the trigeminal nerve. Even mild pressure applied at the projection of the cliary body may cause extreme pain. Numerous self-defense manuals recommend pressing on the globe at this anatomic projection as the last resort. Irritation of the ciliary processes causes intensive cyclitic pain that is felt deep in the eye with pressure sensation [2].

Anatomical structures of the eye are innervated partially through trigeminal nerve branches. The ophthalmic, or first division of the trigeminal nerve, splits into frontal, nasociliary and lacrimal branches which contribute to innervation of ophthalmic and periorbital areas. The maxillary, or second division, partially innervates the periorbital area [3].

There is no unified classification for the clinical spectrum of ophthalmalgia. Ophthalmalgia syndrome can be divided into two types on the basis of anatomy: anterior (the cornea and ciliary body) and posterior (the optic nerve and retrobulbar space). Pain can be categorized by location into retrobulbar, periorbital, retroorbital and facial [4].

The following are noteworthy among the ophthalmic and neuro-ophthalmic causes of the pain syndrome: (1) acute angle-closure glaucoma, (2) incorrectable astigmatism, (3) infectious disease (blepharitis, hordeolum, conjunctivitis, corneal erosion or ulcer, iridocyclitis,

dacryoadenitis, episcleritis or scleritis), (4) intraocular foreign body, (5) eye burns, (6) visual fatigue syndrome, (7) dry eye syndrome, (8) herpes zoster ophthalmicus, (9) optic nerve pathology (optic neuritis or compressive optic neuropathy), and (10) orbital disease (inflammation, neoplasms or pseudotumors).

Extraocular causes of ophthalmalgia are variable and require a detailed differential diagnosis made by a multidisciplinary team comprising, besides the ophthalmologist, the neurologist, neurosurgeon, oral and maxillofacial surgeon, etc. Among the common causes of the syndrome are (1) headache, (2) post-inflammatory or cancer-related trigeminal neuropathy, (3) intracranial processes (like tumors, pseudotumors, venous sinus thrombosis), (4) vascular pathology of the cavernous sinus or superior orbital fissure, (5) pain radiating to the eye and caused neither by ocular nor by cranial disease (but, e.g., by dental or jaw pathology), and (6) a number of comorbidities associated with oculofacial pain (fibromyalgia, blepharospasm, peripheral neuropathy, Sjogren's syndrome) [1].

A rise in intraocular pressure (IOP) in the eye with glaucoma can be followed by pain syndrome radiating to the tissues surrounding the eye. Signs of elevated IOP may vary from obscure ocular discomfort to extremely intense pain radiating to the forehead, supraorbital ridge, parietal region and mastoid process. In addition, the pain sometimes spreads in a hemicranial pattern, although some patients with elevated IOP report no symptoms [5]. Furthermore, a short-term rise in IOP to 60 mm Hg after intravitreal drug administration is not generally accompanied by pain [2, 5].

An acute attack of angle-closure glaucoma is always accompanied by such symptoms as unilateral headache, eye pain, reduced heart rate, nausea, vomiting, abdominal pain, reduced vision, halos, mixed conjunctival injection, corneal edema, mydriasis, and firmness with painless palpation of the eye. The diagnosis of angle-closure glaucoma is challenging if abdominal pain, nausea, and ocular headache are more marked than ocular symptoms [6, 7].

Hypertensive pain syndrome may also develop in patients with terminal glaucoma. An underlying cause for its development, however, remains not fully elucidated since there is no relationship between the IOP and amount of pain. The syndrome develops (1) in patients with terminal glaucoma and (2) often in the presence of a somatic disease in those with secondary glaucoma who have low or absent visual functions. Under these circumstances, the patient experiences the nagging, aching, and dull pain that (1) radiates to the supraorbital area and cheek bone, (2) sometimes spreads in a hemicranial pattern, and (3) is poorly responsive to treatment with non-narcotic analgetics. Carboanhydrase inhibitors have been reported to temporarily improve the condition [2].

Two types of pain can be distinguished in the cornea: nociceptive and neuropathic pain [8]. Nociceptive pain results from tissue damage or inflammation caused by trauma, air pollution, elevated tear osmolarity, etc. Neuropathic pain results from tissue damage or somatosensory disorders and is mostly chronic [9].

Dry eye disease (DED) is a common disorder whose most consistent feature is chronic dry eye-like pain (DELP) [10]. Both nociceptive pain and neuropathic pain develop in DED.

Specific corneal nociceptors (TRPM8) play a key role in the development of chronic sensations of dryness, foreign body, burning and pain [11-13]. There are pathologic conditions characterized by hyperalgesia (i.e., increased sensitivity and responsiveness of nociceptors to their noxious stimuli). Reduced tear production in DED, prolonged contact lens wearing, and eye condition after keratorefractive surgery are factors playing a role in the development of corneal hyperalgesia [14].

Corneal syndrome develops in numerous corneal disorders (traumatic erosion, burns, and keratites), and the pain is more severe compared to DED. In addition, the ocular pain is acute, stabbing, and stitching, and is always accompanied by photophobia, tearing and blepharospasm. Treatment with topical ocular anesthetics (including Alcaine) can temporarily improve the pain.

Uveitis can be divided into iritis, cyclitis (ciliary body inflammation), and iridocyclitis. A pain syndrome of varying degree can develop with ciliary process involvement. Patients with this syndrome commonly exhibit sudden, sharp and intense pain in the eye and/or orbito-frontal areas, with conjunctival hyperemia, photophobia, and blurred vision. In addition, there is pain on palpation of the globe, although the globe is tender to palpation.

Scleritis (inflammation of the sclera) is also accompanied by eye pain. Thirty-nine to 50 percent of patients with scletitis have rheumatological disorders [15, 16]. Pain onset is gradual. Pain is acute, localized and intense, and often can be described as a deep boring ache that intensifies with movement of the globe. There is localized pain on palpation of the globe. The disease is often accompanied by intense headache which makes diagnosing the condition particularly challenging. The associated ocular symptoms include tearing, blurred vision and red eye. A detailed eye examination reveals local scleral hyperemia and dilated deep episcleral vessels.

Posterior scleritis is a less common cause of eye pain, and most frequently found in middle-aged women. Pain occurs with movement of the globe, radiates to the periorbital area, and is accompanied by a reduction in visual acuity. It is usually described as penetrating in character and radiating to the head, temple, and cheek bone area [17]. In the International Headache Society Classification it is included in the section "Headache attributed to ocular inflammatory disorder" [18].

Optic neuritis is characterized by sudden vision loss, impairment of accurate color vision (with regard to red and green colors), and pain on eye movement [4]. Inflammation of the optic nerve can be associated with

systemic autoimmune disorders and demyelination [19-22]. Eye pain does not develop in localized optic nerve inflammation, and pain syndrome arises only when nerve sheath involvement is present. Retrobulbar neuritis may produce pain on eye movement, since the optic nerve is encircled by the annulus of Zinn at the location where it enters the optic canal. Besides pain, patients with the disease commonly report discomfort on touching the eye and photopsia. However, patients with vascular optic nerve disorders (ischemic optic neuropathy) complain of eye pain less frequently (only 10%) [23].

Patients with orbital pathology commonly report both ocular and periorbital pain that is exacerbated by ocular movements [24, 25]. Orbital inflammation, neoplasms, pseudotumors and vascular damage are also manifested by exophthalmos, conjunctival injection, ocular motility abnormalities and diplopia.

Tolosa-Hunt Syndrome is a rare ocular disease associated with pain in the eye. The disease is caused by inflammatory granulomatous infiltration of the superior orbital fissure or cavernous sinus and is manifested by unilateral orbital or periorbital pain and ophthalmoplegia involving cranial nerve (CN) III more frequently than CN IV or CN VI [26].

As mentioned above, generally, patients with inflammatory orbit disorders express clinical manifestations (exophthalmos, ophthalmoplegia and red eye). In some cases (like those of orbital myositis), however, external examination finds no change in ocular structures. Patients with orbital myositis exhibit moderately intense intraocular pain that is always exacerbated by eye movement. The disease occurs most frequently in young to middle-aged adults with a female predominance. Echography in orbital myositis may reveal enlarged and thickened extraocular muscles, although these symptoms are not specific [27-29]. The disease is usually treated with systemic non-steroidal anti-inflammatory drugs.

Trigeminal neuralgia causes extremely severe "electric-shock-like" pain in the eye, since the latter is innervated by trigeminal nerve branches. The disease is characterized by brief attacks of severe pain that is paroxysmal and sharp, usually occurring in multiple bursts in rapid succession lasting a few seconds. Pain-related complaints in some patients with trigeminal neuralgia may involve only attacks of localized ocular pain which can be triggered by stimulation such as tooth brushing, articulation, make-up, hair combing [3].

Supraorbital neuralgia is a type of trigeminal pain syndrome. The pain of supraorbital neuralgia is characterized as paroxysmal or constant pain in the region of the supraorbital notch and the medial aspect of the forehead of the area supplied by the supraorbital nerve, which is the largest branch of the ophthalmic nerve (the first branch of the trigimental nerve) [30]. Intense paroxysmal pain is accompanied by pain felt in the region of the supraorbital notch which is abolished by local anesthetic blockade. The pain of infraorbital neuralgia is characterized as paroxysmal intense pain in the territory supplied by the infraorbital nerve. Application of external, brief, pressure in the head, such as those produced by a band around the head or swimming goggles, may give rise to a headache with the development of supraorbital neuralgia [31].

Ocular symptoms and visual abnormalities are common in patients with a headache. According to ICHD [18], migraine and trigeminal autonomic cephalalgias are the primary headaches frequently associated with ocular manifestations. Trigeminal autonomic cephalalgias include cluster headache, paroxysmal hemicranias, short-lasting unilateral neuralgiform headache attacks, and hemicrania continua. Short-lasting unilateral neuralgiform headache attacks are subdivided into those with conjunctival injection and tearing (SUNCT) and those with cranial autonomic symptoms (SUNA) [18].

Migraine can be accompanied by such ocular manifestations as eye pain, visual abnormalities and ophthalmoplegia. Aura has been found in 15-20% of patients with migraine, and commonly precedes migraine headache [32].

Subacute angle closure should be included in the differential diagnosis of patients older than 50 years with a new-onset short-lasting (<4 hours) headache meeting some of the criteria for migraine. The ocular symptoms include glaucomatous optic nerve damage, elevated IOP, and close or narrow angle by gonioscopy [33].

In patients with ophthalmoplegic migraine, migrainous headache is associated with periorbital pain. Pain is accompanied by paresis of one or more of the ocular motor nerves (commonly, one nerve) and the absence of intracranial injury [34, 35].

The trigeminal autonomic cephalalgias (cluster headache, paroxysmal hemicranias, SUNCT/SUNA, and hemicrania continua) share the clinical features of an intense unilateral headache that can be either retro-orbital or peri-orbital. One of the diagnostic criteria for any trigeminal autonomic cephalalgia is at least one of the following symptoms or signs, ipsilateral to the headache: (a) conjunctival injection and/or lacrimation, (b) nasal congestion and/or rhinorrhoea, (c) eyelid edema, (d) forehead and facial sweating, (e) forehead and facial flushing, (f) sensation of fullness in the ear, and (g) miosis and/or ptosis [18, 36].

Cluster headache is the most common type of trigeminal autonomic cephalalgia. It is (a) characterized by attacks of severe, strictly unilateral pain which is orbital or supraorbital, and (b) associated with ipsilateral conjunctival injection, lacrimation, nasal congestion, rhinorrhoea, forehead and facial sweating, miosis, ptosis and/or eyelid edema, and/or with restlessness or agitation [18]. These attacks last 15–180 minutes and occur from once every other day to eight times a day. Cluster headache is commonly found in male smokers aged 30-40 years. The attacks tend to occur with great regularity at the same time of day (e.g. they can wake the patient up like an alarm

clock after falling asleep) and are commonly associated with agitation [37].

Paroxysmal hemicrania is somewhat clinically similar to cluster headache, and is characterized by intense unilateral orbital or suptaorbital pain, too. Its attacks last 2–30 minutes and occur 5–40 times a day, and respond absolutely to indomethacin. It is commonly found in women aged 20-30 years [18, 36].

SUNCT syndrome is characterized by attacks of electric-shock like pain with orbital or periorbital distribution, lasting for 5–250 seconds and occurring with a frequency of ≤ 200 a day [38].

Hemicrania continua are characterized by moderate to severe pain lasting for ≥ 1 day which is frequently associated with eyelid edema. They respond absolutely to therapeutic doses of indomethacin [18].

Cervicogenic headache is defined [18] as headache caused by a disorder of the cervical spine and its component bony, disc and/or soft tissue elements, usually but not invariably accompanied by neck pain. In addition [18], it may be abolished following diagnostic blockade of a relevant cervical structure or its nerve supply.

The spinal nucleus of the trigeminal nerve is located in the medulla oblongata, and approaches superior spinal components thus forming tractus spinalis n. trigeminis. In patients with cervicogenic headache, eye pain is variable in nature (boring, pressing, or neuralgia-like) and usually unilateral. Palpation along the course of the greater occipital nerve elicits localized pain in the neck and increases eye pain from side of palpation. Painful symptoms are substantially relieved by greater occipital nerve block with lidocaine 1% [40].

Carotidynia is a syndrome characterized by long-lasting nagging pain in a half of the neck (usually, in the upper half) which radiates to the eye, face and mandibular jaw. It may be found in internal carotid artery dissection, temporal arteritis, and carotid artery compression by tumor [41].

Patients with intracranial vascular disorders are also sometimes referred to the ophthalmologist. Transient ischemic brain attacks can be accompanied by reduced vision in one eye and ocular pain. As ophthalmic branches of the trigeminal nerve partially innervate supratentorial vessels and dura mater, the pain may radiate to the forehead, ocular and temple regions. According to Gorelick et al [42], 25% of patients with an internal or middle cerebral artery insult have pain at these areas.

A transient rise in intracranial pressure is accompanied by headache and sometimes ocular pain, and has been observed during coughing, sneezing, rising heavy weight, and/or bending over. In some cases, it may be a manifestation of intracranial disease (Arnold–Chiari malformation, posterior fossa tumor, cerebral aneurysm, or stenosis of the internal intracranial artery) [41, 43].

Painful ophthalmoplegia may be seen in patients with vascular disorders such as aneurysm, carotid-cavernous fistula, giant cell arteritis, orbital pseudotumor and Tolosa-Hunt syndrome [26].

In addition to the pain syndrome, patients with carotid-cavernous fistula may exhibit conjunctival injection or chemosis with dilated veins (so called “red eye”), eyelid edema, moderate exophthalmos, elevated IOP and ophthalmoplegia. Pain rarely precedes ocular symptoms [42].

Giant cell arteritis (GCA, also known as Horton disease) is an infectious arterial disease. In addition to systemic symptoms of fever, headache, and muscular and facial pain, GCA may cause ocular pain due to orbital ischemia. GCA is a disorder of old people, predominantly women. The diagnosis is confirmed by biopsy of the affected artery and laboratory tests (complete blood count and blood biochemistry tests). The ocular pain may be accompanied by reduced visual acuity due to ischemic optic neuropathy [44].

There are a number of disorders that are not associated with ocular or intracranial pathology, but may be accompanied by ocular pain. They include, in particular, inflammatory diseases of the paranasal sinuses (frontal, ethmoid and sphenoid sinusitis) which may be associated with a history of recurrent inflammation, paranasal sinus puncture, etc. The pain is usually dull and nagging. As teeth and jaws are structures anatomically close to the eye, their pathologies may be manifested as pain radiating to the eye.

As ophthalmalgia may accompany both ocular and non-ocular diseases, the diagnosis and optimal management of patients with ocular and/or periorbital pain requires a multidisciplinary approach with contributions from ophthalmology, neuro-ophthalmology, neurology, neurosurgery, otoneurology, as well as other medical fields. Early and accurate diagnosis is a prerequisite for proper treatment and prevention of irreversible changes.

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