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Neuroimaging in the Diagnostic Evaluation of Eye Pain

Gabriella Szatmáry[1]

Abstract Ocular or eye pain is a frequent complaint encountered not only by eye care providers but neurologists. Isolated eye pain is non-specific and non-localizing; therefore, it poses significant differential diagnostic problems. A wide range of neurologic and ophthalmic disorders may cause pain in, around, or behind the eye. These include ocular and orbital diseases and primary and secondary headaches. In patients presenting with an isolated and chronic eye pain, neuroimaging is usually normal. However, at the beginning of a disease process or in low-grade disease, the eye may appear "quiet," misleading a provider lacking familiarity with underlying disorders and high index of clinical suspicion. Delayed diagnosis of some neuro-ophthalmic causes of eye pain could result in significant neurologic and ophthalmic morbidity, conceivably even mortality. This article reviews some recent advances in imaging of the eye, the orbit, and the brain, as well as research in which neuroimaging has advanced the discovery of the underlying pathophysiology and the complex differential diagnosis of eye pain.

Keywords Eye pain · Secondary ocular pain · Retro-orbital headache · Neuroimaging · MRI · CT

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✉ Gabriella Szatmáry
gszatmary@yahoo.com

1   Hattiesburg Clinic, PA, 415 28th Avenue, Hattiesburg, MS 39401, USA

Introduction

Ocular pain is defined as pain in the eyeball itself, but this localization is often uncertain; therefore, the term eye pain is frequently used to denote pain in, around, or behind the eye. In general, a patient referred to the neurologist for eye pain has an isolated and "quiet eye" with intra-, peri-, or retro-orbital pain that is often chronic and maybe associated with a headache [1••]. When the neuro-ophthalmic exam is normal, orbital and brain neuroimaging, including CT and MRI, is usually also normal, or it may show incidental findings, such as chronic, non-specific white matter signal changes, or atrophy, depending on the patient's comorbidity and age [2, 3]. However, when the eye pain is non-isolated, but associated with abnormal external appearance, anisocoria, visual loss, or ophthalmoplegia, then neuroimaging is often the test of choice [4]. Neuroimaging may particularly be helpful at the early stage or in low-grade disease processes before other deficits develop [5]. The inflammatory and infectious, mechanical (abnormal intraocular or intracranial pressure), and vascular etiologies, and less likely tumors give rise to a painful eye. According to the site of the underlying pathology, the discomfort may arise from the eyeball, or the orbit, or be referred from the face or head and neck to the eye. This article focuses on the most frequent disorders presenting with eye pain to the neurologist, especially where neuroimaging is either diagnostic or excludes a structural lesion. However, when the diagnosis is clinically secured and an underlying pathology is not suspected, then imaging usually is not required [6].

Neuroimaging-Based Neuroanatomy of Eye Pain

Because the eye (conjunctiva, cornea, sclera, upper eyelid), the forehead, the tip of the nose, the scalp, the dura (anterior cranial fossa, falx cerebri, tentorium cerebelli), and the

intracranial arteries and veins are all innervated by the first division of the trigeminal nerve (V1, ophthalmic), any painful process of these structures can cause eye pain. The ophthalmic branch is purely sensory. Its afferent fibers travel to the complex trigeminal nuclei in the dorsal brainstem, which expand as the trigeminal tract between the midbrain and upper cervical spinal cord at the level of C2 [7]. Familiarity with the anatomy of the pain pathway may allow the diagnosis of isolated eye pain by discovering subtle pathological changes. For example, Siritho reported a challenging case of herpes zoster ophthalmicus presenting without rash [8]. In another reported case, diffusion tensor MRI-derived fiber tractography and functional MRI were successfully used to detect brainstem dysfunction in patients with chronic temporomandibular pain syndromes [9, 10]. In a third example, a pontine descending tractotomy was done using imaging-based, neuronavigation-assisted microsurgery to help patients with medically and surgically intractable trigeminal neuralgia [11].

Neuroimaging in Neuro-Ophthalmology: Technical Considerations

MRI is the modality of choice when either neurologic or ophthalmic cause of eye pain is suspected. It provides non-invasiveness, full field of view imaging, high resolution, soft tissue contrast, and radiation-free benefits. Although MRI is a sensitive technique, its specificity is relatively low. For example, diffusion-weighted imaging (DWI), originally thought to be specific for vascular etiology, has been reported to show reduced diffusivity (suggesting axonal degeneration) in several diseases affecting the optic nerve and optic nerve head [12, 13]. Neuroimaging of the orbit poses technical challenges related to several factors; these include the artifacts arising at the different tissue interfaces and the techniques utilized for better visualization (fat suppression). A promising technique for orbital imaging is 3D radial-volumetric-interpolated breath-hold examination (VIBE). This is a motion robust fat-suppressed (FS), gradient echo, high-resolution (0.5–1 mm) isotropic sequence [14]. Another likely technique is 3D high-resolution MR angiography (MRA) with binomial off-resonant rectangular (BORR) pulse for imaging the orbital vasculature [15]. CT is helpful in the evaluation of calcified lesions such as aneurysm, optic nerve head drusen, optic nerve sheath meningioma, and retinoblastoma. However, it is limited by radiation exposure. Other techniques utilized in neuro-ophthalmology, often in conjunction with MRI, include optical coherence tomography (OCT) of the optic disc and the macula [16, 17], and chairside dynamic ophthalmic ultrasonography, which provides non-invasive evaluation of a variety of ocular and orbital pathologies [18].

Ophthalmic Causes of Eye Pain

Ophthalmic causes of eye pain may be divided into superficial and deep ocular, orbital (intra-and extraconal, muscle cone), and referred pain [19]. Features suggesting superficial eye pain include foreign body sensation, itching, and pain provoked by palpation. Photophobia can be associated with both superficial and deep eye pain and neurological disorders (most frequently migraine) [20, 21].

The most frequent ophthalmic cause of eye pain is chronic dry eye disease, a type of neuropathic ocular pain [22, 23]. In the neuropathic dry eye, orbital and brain MRI shows no relevant abnormality. However, familiarity with the condition is important for differential diagnostic purposes. From the imaging standpoint, the test of choice is corneal confocal microscopy, which allows direct observation of the corneal nerve endings, which show decreased density in patients with dry eye disease and with chronic migraine [24]. Neuropathic ocular pain has also been described following retina surgery and enucleation (phantom eye syndrome). Ophthalmic causes of referred eye pain or strain include refractive errors, accommodation spasm, anisometropia, astigmatism, and uncorrected presbyopia, especially in association with dry eye disease.

Infectious-Inflammatory Pain

Ocular pain provoked by eye movement suggests an orbital inflammatory, demyelinating, or infectious process, such as optic neuritis or perineuritis, scleritis, trochleitis, or orbital myositis. Posterior scleritis may be associated with anterior optic perineuritis, choroidal folds or effusion, serous retinal detachment, or macular edema. Orbital ultrasonography is very sensitive in detecting the associated posterior sub-tenon's fluid accumulation [18], but MRI or CT with and without contrast is recommended as the initial diagnostic study [25]. Thin-section axial contrast-enhanced (CE) T1W FS sequence typically demonstrates thickening and enhancement of the posterior sclera. Patients with trochleitis present with severe episodic uni- or bilateral ocular or peri-ocular ache that worsens on adduction in downgaze, with greatest discomfort at the superomedial orbital rim. It may herald an autoimmune disorder [26]. MRI and CT high-resolution images may show thickening and enhancement of the trochlea or the tendon of the superior oblique muscle. It should be differentiated from trochlear headaches [27].

Optic perineuritis (OPN) is a localized form of idiopathic orbital inflammatory disease, in which the specific target tissue is the optic nerve sheath. It can be confirmed by demonstrating peripheral thickening and enhancement of the involved optic nerve sheath without central (nerve) involvement on CE MRI FS sequence [28••]. Perineuritis may be isolated or associated with myositis, posterior scleritis, or inflammatory changes in the adjacent intraconal adipose tissue, which is

suggested by enlargement and enhancement of these structures. OPN may be idiopathic or associated with a systemic disorder, such as Bechet's disease, Lyme disease, and sarcoidosis [29]. In demyelinating optic neuritis (ON), pain on eye movement was reported by 95 % of patients in the Optic Neuritis Treatment Trial, typically presenting few days prior to the ipsilateral visual loss and subsiding after the onset of blurred vision. In anterior optic neuritis, optic disc protrusion into the posterior globe may be observed on MRI with enhancement depending on the degree of disc swelling, similarly to optic disc edema due to other causes, such as anterior ischemic optic neuropathy or papilledema. Typically, mild optic nerve enlargement with intrinsic T2 hyperintensity and enhancement of the affected optic nerve is seen [30]. The hyperintensity is best demonstrated on MRI STIR, T2 FLAIR-, or T2-weighted (T2W) FS sequences, while the enhancement is best evaluated on CE T1W FS sequence. Occasionally, optic nerve hyperintensity on DWI, with or without corresponding hypointensity on the apparent diffusion coefficient (ADC) map, has also been observed [12] and is consistent with water restriction, similar to ischemic optic neuropathy. MRI is not required for the diagnosis of optic neuritis, which is made clinically. However, MRI is the only tool that enables the physician to diagnose multiple sclerosis at the first clinical presentation by identifying spatial and temporal dissemination. In neuromyelitis optica (NMO), the optic neuritis may be uni- or bilateral, although the bilaterality or chiasmal involvement may only be appreciated on MRI [30]. NMO patients with myelopathy typically demonstrate an elongated segment (three or more vertebral body segments) of continuous cord T2 hyperintensity, the so-called longitudinal extensive transverse myelitis. This is contrary to MS lesions, which are short (less than one vertebral body segment) and scattered. The lesion shows enhancement when the disease is active, although this may persist for up to 4 months after a relapse. In neurosarcoidosis, the associated eye pain may be secondary to optic neuritis, an inflamed lacrimal gland, uveitis, or may be referred from the intracranial compartment [31]. On MRI, sarcoidosis-related ON may be undifferentiated from any other causes of ON, but additional lacrimal gland enlargement suggests the diagnosis. Frohman et al. reported the so-called stem-to-stern (from globe to chiasm) optic nerve enhancement or nodular non-contiguous involvement. In the presence of frontal basilar meningeal enhancement, this is very suggestive of sarcoidosis [32]. Idiopathic orbital inflammation (IOI) or orbital pseudotumor may be localized or diffuse. In suspected isolated orbital myositis, a localized form of IOI, MRI, or CT with and without contrast is the test of choice [33•], but the disease could be followed by orbital ultrasonography [18]. In isolated myositis, neuroimaging usually shows enlargement of the affected extraocular muscle with involvement of the tendinous insertion site. There is a broad imaging differential diagnosis,

especially in diffuse IOI, including but not limited to lymphoma, IgG4-related orbital disease (IgG4-ROD) [34], orbital histiocytic disorders (e.g., Rosai-Dorfman and Erdheim-Chester disease, Langerhans' cell histiocytosis) [35], orbital amyloidosis [36], and Tolosa-Hunt syndrome (THS) [37]. Any of these disorders may spread intracranially mimicking a meningioma or even a glioma [38, 39]. The MRI findings are nonspecific and include homogeneous T1W isointensity and T2W hypo- or isointensity (suggesting high cellularity of the lesions) and homogeneous enhancement. Helpful signs that suggest IgG4-ROD include findings that it is typically painless [40], is often bilateral and involving the lacrimal and salivary glands, frequently causes infraorbital nerve enlargement (a pathognomic feature) [41], is associated with multimuscle extraocular myositis and compressive optic neuropathy, may be a sclerosing orbital inflammation [42], and presents with an intracranial manifestation such as hypophysitis and hypertrophic pachymeningitis. On the contrary, IOI is typically associated with severe eye pain, restriction of eye movement in the field of action of the affected muscles, and orbital myositis of one or two muscles (most frequently: medial > superior > lateral > inferior rectus).

Pain in and around the eye may be the presenting symptom of orbital granulomatosis with polyangiitis (Wegener's granulomatosis); neuroimaging characteristically reveals paranasal sinus disease with bony erosion and orbital extension [43].

Fungal infections, especially in diabetic patients, may present with severe ocular or periorbital pain even without external infectious signs. Therefore, in the appropriate clinical settings, early sinonasal endoscopy with biopsy should be pursued to exclude rhino-orbital mucormycosis with the risk of intracranial spread or aspergillosis [44, 45]. Graves' disease is the most frequent cause of thyroid eye disease (TED) and may present with ocular, orbital, or periorbital pain in a "quiet" eye. MRI has the advantage over CT by allow staging of the disease, as T2 hyperintensity of the most frequently involved muscles (inferior and medial rectus) suggests an active disease that is more amenable to treatment with corticosteroids [46] (Fig. 1). More recently, Kilicarslan et al. found DWI to be helpful in the detection of extraocular muscle involvement in the early stage of TED [47]. In TED, there is typically thickening and enhancement of the muscle itself, contrary to myositis where the muscle tendon is also involved.

Mechanical Causes of Eye Pain (Glaucoma)

When the intraocular pressure is above 40 mmHg in an otherwise quiet eye, it may cause ocular or periocular pain or non-localizing episodic headache. This is especially true for patients with subacute angle-closure glaucoma, which may result in a significant delay in diagnosis [48, 49]. Therefore, glaucoma should be included in the differential diagnosis of an adult patient presenting with new onset headache. Because

Fig. 1 Forty-two-year-old woman presented with binocular diplopia and "soreness" of both eyes. Coronal T2-weighted image demonstrates enlargement and heterogeneous signal of the medial more than lateral rectus muscles bilaterally at the mid-orbital level (**a**), and corresponding contrast-enhanced T1-weighted image (**b**) shows heterogeneous enhancement, more in the T2 hyperintense peripheral areas (*arrows*, marked in the right orbit only). The T2 hyperintensity suggests higher water content, consistent with active stage of thyroid eye disease
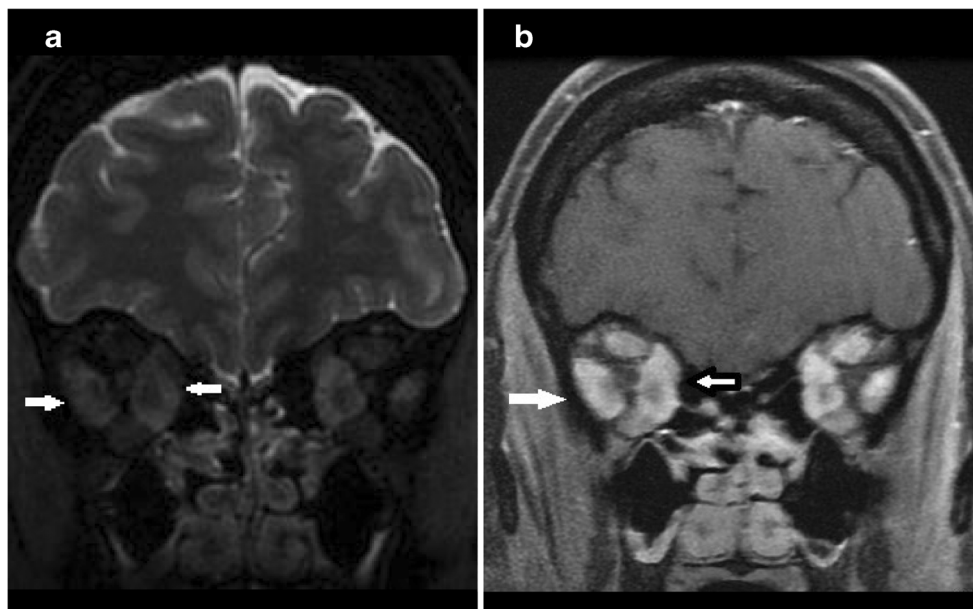
it is rare to provoke a glaucoma attach with the use of mydriatic drops, this fear should not discourage the neurologist to perform a dilated fundus examination [1••]. MRI is usually normal in new onset glaucoma patients; however, in association with chronic primary open-angle and more recently even early stages of glaucoma, several brain changes have been noted. These include atrophy and signal changes in the lateral geniculate body and decreased response on fMRI [50••, 51]. These imaging modalities are especially promising for securing the diagnosis in normal-tension glaucoma.

Vascular Pain

Following strabismus or surgery for scleral buckling, the development of achy pain may herald anterior segment ischemia. In any vascular lesion of the orbit, ocular or periocular pain may be the prodrome of a neuro-ophthalmic deficit, such as in ischemic optic neuropathy and microvascular ocular motor cranial nerve palsy. In ischemic optic neuropathy, MRI may demonstrate water restriction in the optic nerve on DWI [12], and in microvascular ocular motor cranial nerve palsy, it may show chronic microvascular changes of the brain or be normal.

Tumor-Related Pain

Ocular tumors usually present with painless visual disturbance but occasionally with pain in a "quiet eye." Primary orbital tumors (eyelid, lacrimal gland) may also present with isolated eye pain (e.g., in lacrimal gland tumor, the eye pain may antecedes proptosis and gaze-evoked amaurosis) [52]. The differential diagnosis of lacrimal gland lesions includes

pleomorphic adenoma (the most common benign tumor; however, malignant transformation may occur), adenoid cystic carcinoma (the most frequent malignant tumor), lymphoma (often a mucosa-associated lymphoid tissue type), and adenocarcinoma [53••]. CT may show calcification in pleomorphic adenoma and adenoid cystic carcinoma, but associated bone erosion and infiltration of adjacent structures only occurs in a malignancy. Adenoid cystic carcinoma may recur even after orbital exenteration and usually involves contiguous structures, such as the cavernous sinus secondary to perineural or perivascular spread. Other primary orbital tumors tend to present with painless visual symptoms and include cavernous hemangioma, lymphangioma, schwannoma, optic nerve glioma, and optic nerve sheath meningioma [52]. Tumorous processes of orbital bone may cause referred pain to the eye and include fibrous dysplasia, aneurysmal bone cyst, and chondrosarcoma.

Secondary orbital tumors that spread by direct extension from contiguous structures, especially in the immunocompromised, include cutaneous squamous cell carcinoma of the head and neck. Secondary metastatic orbital tumors have a predilection for highly vascular tissues (choroid, extraocular muscle, or marrow space of the greater wing of the sphenoid). Tumors that tend to metastasize to the orbital compartment include bladder, breast, lung, GI and prostate cancer, and lymphoma. On MRI, the lesion is usually hypointense on T1W and shows variable signal on T2W sequence (darker signal suggest higher cellularity) and enlargement and enhancement of the involved orbital structures. The most frequent skull base tumors that spread to the orbital compartment by direct extension from contiguous structures include nasopharyngeal carcinoma, angiofibroma, and esthesioneuroblastoma.

Neurologic Causes of Eye Pain

In general, any neurological disorder can cause referred eye pain, such as disorders of the cervical spine, carotid artery, sinuses [54], or temporomandibular joint. Therefore, neuroimaging should be obtained only when an underlying causative lesion is suspected, based on the patient's history and neuro-ophthalmic examination [2]. This section will be limited to the retro-orbital pathologies with potential neuro-ophthalmic complications.

Primary Headache Disorders

The most frequent neurological cause of eye pain is migraine [1••, 3, 24], followed by primary stabbing headaches, trigeminal autonomic cephalalgias, and epicrania fugax [55]. A neuroimaging study is not indicated for the diagnosis of a primary headache disorder. However, when first evaluating a patient with new onset pain that localizes to the orbital region, especially when associated with autonomic features, then imaging is recommended to exclude cluster mimics, such as infection, tumor, and other pathologies [56]. Also, when a primary stabbing headache is persistently restricted to the same location, an underlying structural lesion in that location or within the distribution of the affected cranial nerve should be excluded by an imaging study.

Secondary Headache Disorders

The secondary causes of headaches and their neuroimaging features were recently reviewed in this journal by Chaudhry et al. Most of the reviewed disorders can be associated with referred ocular or periocular pain [57••].

Infectious-Inflammatory Pain

Cavernous sinus syndrome (CSS) can be caused by any pathology involving the cavernous sinus, but an infectious or inflammatory process is the most likely to present with intra- or periorbital pain before other more localizing signs appear. Most of the pathologies involving the cavernous sinus have the potential to involve adjacent structures, including the superior orbital fissure and orbital apex. Hence, the differential diagnosis of CSS includes disorders described under IOI, in addition to lymphoma, meningioma, sarcoidosis, THS, and less frequently Lemierre syndrome. Lemierre syndrome is a thrombophlebitis due to infection, typically untreated periodontal disease. This results in uni- or bilateral cavernous sinus thrombosis and may cause DWI hyperintensity in the superior ophthalmic vein(s) [58]. The diagnosis of THS is a diagnosis that is largely based on neuroimaging by excluding other disorders and demonstrating an inflammatory lesion [37]; however, recently reports of THS with normal MRI have been described [59]. THS typically presents with episodic but progressive eye pain, followed by diplopia. MRI with high-resolution images through the orbital apex and cavernous sinus demonstrates widening, T2 hyperintensity, and enhancement in the cavernous sinus, superior orbital fissure, and orbital apex; narrowing of the ipsilateral intracavernous internal carotid artery; and enlargement of the optic nerve and extraocular muscles. After initiation of high-dose corticosteroid treatment, symptoms should resolve within 24–72 h; however, improvement of cranial nerve deficits and regression of MRI abnormalities may take 2–8 weeks. CNS involvement is seen in about 25 % of sarcoidosis cases, but many of these are subclinical. Sarcoidosis is named the master mimicker of several disorders clinically and on imaging because it has a wide spectrum of intracranial imaging appearances. On brain MRI, lesions tend to be isointense relative to gray matter on T1W and hypointense on T2W sequences, with thickening and enhancement of the affected structures. Typical sites of involvement include the dura and leptomeninges at base of the brain, hypothalamus, pituitary gland, infundibulum, and anterior visual pathway [32]. Typical pattern of involvement suggesting sarcoidosis includes granulomatous infiltration causing intense plaque-like or nodular dural and leptomeningeal thickening and enhancement and solitary or multifocal CNS and meningioma-like dural masses. Leptomeningeal granulomas may go unnoticed on non-CE MRI.

Mechanical (Abnormal Intracranial Pressure)

Change in intracranial pressure in any direction can cause a headache but not typically ocular pain. Spontaneous intracranial hypotension is characteristically associated with orthostatic, while intracranial hypertension with hydrocephalus with occipital headache. Intracranial hypertension without hydrocephalus, i.e., pseudotumor cerebri syndrome (PTCS), frequently presents with retro-ocular pain, which may increase on eye movements [60], but the headache could be in any location [61]. PTCS is either primary, so-called idiopathic intracranial hypertension or secondary when an underlying cause is identified; therefore, it is a diagnosis of exclusion. In patients with symptoms suggesting raised intracranial pressure (ICP), a brain MRI with and without contrast should be obtained to exclude a space-occupying lesion, ventriculomegaly, and meningeal enhancement [62]. MRI in a patient with idiopathic intracranial hypertension should be normal, except it may show any of the following structural changes: empty or partial empty sella (usually with enlargement of the sellar floor suggesting chronicity); dilation of the optic nerve sheath; flattening of the posterior sclera with or without protrusion into the eyeball; tortuous course of the intraorbital optic nerve(s); and lateral transverse sinus stenosis (usually bilaterally) on MR or CT venography [63••]. The recognition of these imaging epiphenomena resulted in the newest revision of PTCS

Fig. 2 Twenty-three-year-old woman with history of migraine and 1 week duration of left ear ache presented with the worst headache of her life, described as left-sided with radiation into the neck for 5 days. **a** Head CT without contrast shows hyperdense vascular structures along the left tentorium cerebelli (*white arrow*) and transverse sinus (*red arrow*) that are most consistent with acute cortical vein and venous sinus thrombosis, respectively. **b** Axial gradient echo sequence shows hypointensity in the left transverse and sigmoid sinuses (*white arrow*) consistent with thrombosis and mild, likely reactive, opacification of the left mastoid air cells (*yellow arrow*)
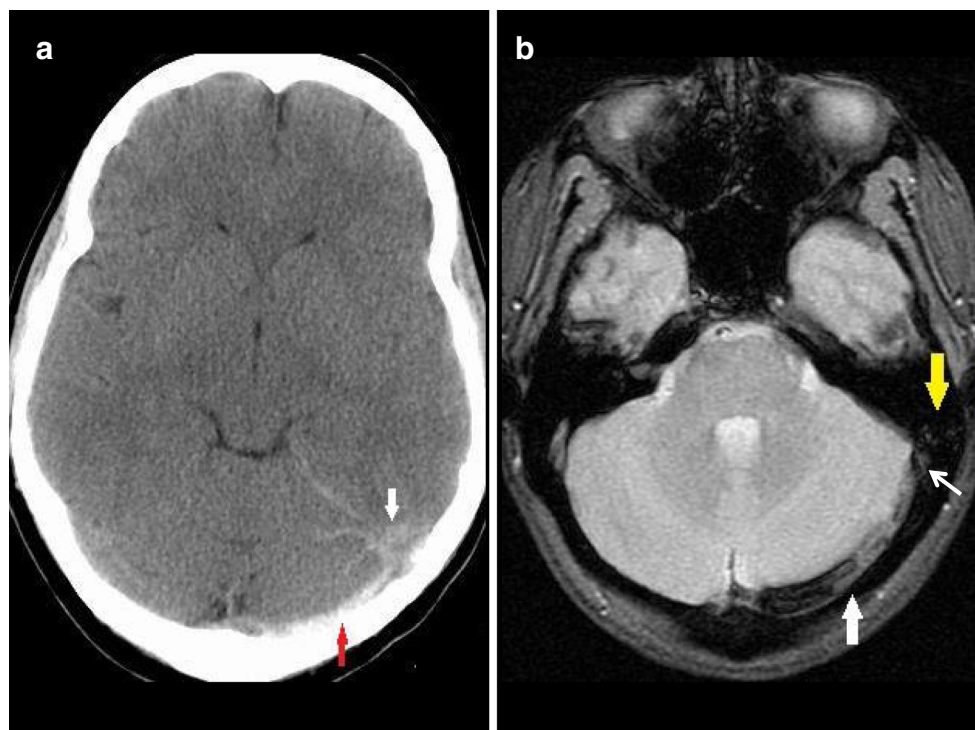
diagnostic criteria [62]. Additional neuroimaging findings that support raised ICP include meningoceles, hyperintensity of the optic disc on DWI [13], and spontaneous CSF leak (most frequently observed at the olfactory recess). In patients with asymmetric papilledema, larger optic canal size on the side of more disc swelling was measured [63••]. Causes of secondary PTCS include cerebral venous sinus occlusion, such as might result from a meningioma adjacent to the superior sagittal sinus, thrombosis (Fig. 2), or giant arachnoid granulation [64]. Spinal leptomeningeal lymphoma may also present as PTCS. Herespinal MRI typically shows extensive leptomeningeal enhancement of the lumbar and cauda equina nerve roots [65]. When a paraganglioma arises from the jugular bulb along the tympanic branch of the glossopharyngeal or the auricular branch of the vagus nerve, it may obstruct the intracranial venous outflow, resulting in secondary PTCS [66].

Vascular Pain

An unruptured supra- or parasellar aneurysm of the internal carotid or ophthalmic arteries may be associated with peri-ocular pain and may cause a compressive optic neuropathy or chiasmopathy. Typically, a MRI T1W image shows an extra-axial, round, and mixed signal lesion, indenting the intracranial optic nerve or chiasm. This corresponds to hypointense flow void on coronal T2W image and peripheral enhancement due to central thrombosis. Only a minority (5 %) of trigeminal neuralgia patients

present with periocular pain due to involvement of the ophthalmic division. Brain MRI is obtained to exclude neurovascular compression of the nerve at the trigeminal root entry zone by the superior cerebellar artery and less frequently a posterior fossa tumor or multiple sclerosis plaques.

Cervical carotid dissection may present with acute onset of ocular pain [67], retro-orbital headaches, and neck pain radiating to the jaw or eye and is frequently associated with ipsilateral Horner [68] syndrome. CT scan of the head without contrast in the acute setting is often interpreted as "normal," but even early on, it may reveal enlargement with central area of hypo-and peripheral hyperdensity of the involved carotid artery at the skull base (Fig. 3a). The imaging evaluation of a suspected Horner syndrome can be lengthy and costly because of the long oculosympathetic pupillomotor pathway; therefore, the imaging study should be chosen according to the suspected site of injury [69]. However, recently, a single CE brain MRI with coverage extending to the T2 vertebral body level was found to be efficacious and cost effective [70]. MRI scan T1, T2, and DWI sequences (Fig. 3b) typically show peripheral hyper- and central hypointensity in the cervical segment of the involved artery with corresponding ADC map hypointensity consistent with water restriction in the vessel wall.

Carotid artery stenosis with resultant ocular hypoperfusion may cause a dull retro-orbital or frontal headache

Fig. 3 Forty-eight-year-old man with history of hypertension presented with new onset, persistent left retro-orbital headaches and an enlarged right pupil for 1 week. **a** Head CT without contrast demonstrates enlargement of the left internal carotid artery (ICA) with central area of hypodensity and peripheral hyperdensity (**a**, *red arrow*) and on corresponding axial diffusion-weighted image peripheral hyperintensity and central area of hypointensity in the left ICA (**b**, *red arrow*), consistent with an acute dissection of the left ICA, and normal right ICA (**a**, *yellow arrow*)
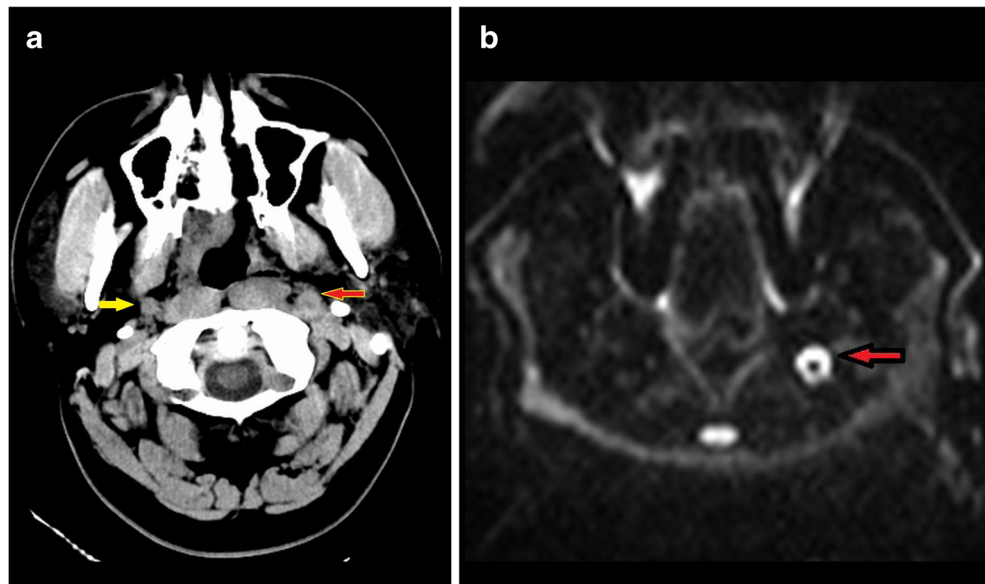
and various fundus abnormalities, consistent with ocular ischemic syndrome [71]. Typically, color Doppler flow imaging of the ophthalmic and central retinal artery demonstrates decreased velocity. Paradoxically, surgery for carotid artery stenosis may result in unilateral headache, with face and eye pain secondary to cerebral hyperperfusion syndrome [72]. Reversible cerebral vasoconstriction syndrome (RCVS) typically presents with an occipital onset bilateral thunderclap headache, followed by a more diffuse pain within a few seconds [73], though the headache may be retro-orbital initially,

and subsequently visual symptoms, such as homonymous hemianopia or Bálint syndrome [74, 75], may develop. Recently, RCVS was found to be the most frequent cause of non-aneurysmal convexal subarachnoid hemorrhage with resultant superficial siderosis that is best observed on susceptibility-weighted or other gradient echo sequences [76].

A carotid-cavernous sinus dural arteriovenous fistula characteristically presents with retro-orbital headaches that may antedate other symptoms by 1–7 months [77]. MRI and MRA head source images frequently show the earliest

Fig. 4 Seventy-five-year-old woman presented with 1-year duration of binocular diplopia and progressive redness of the eyes, right greater than left, for 6 months. **a** Brain MRA scan without contrast source image demonstrates abnormal signal in the right cavernous sinus (*white arrow*), dilated right Sylvian vein (*yellow arrow*), abnormal signal and dilation of the intercavernous sinus (**a**, *red arrow*), and dilation and arterialization of the right superior ophthalmic vein (**b**, *arrow*), consistent with right carotid-cavernous sinus fistula
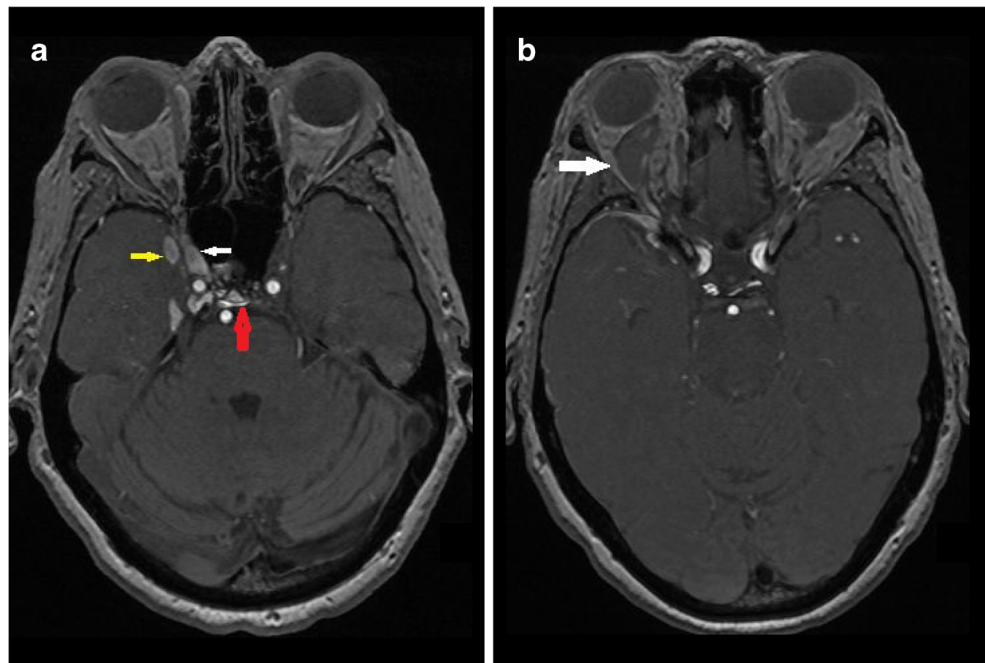
findings: abnormal signal intensity and small flow voids in the cavernous sinus [78] (Fig. 4), asymmetry of the cavernous internal carotid arteries (smaller on the affected side), enlargement of the superior ophthalmic vein with flow void suggests reversed flow (arterialization), and tortuous intracranial ipsilateral hemispheric cortical veins with risk of venous infarction. In addition, the refluxed blood may flow to the contralateral cavernous sinus via the intercavernous sinus and further to the opposite superior ophthalmic vein. Carotid-cavernous fistula is treated with transvenous (with or without transarterial) coiling, depending on the route of refluxed (shunted) blood. Following coiling of the fistula, the periocular pain should resolve.

A patient with giant cell arteritis (temporal arteritis) may present with retro-orbital pain; temporal, frontal, or occipital headache; jaw claudication; scalp tenderness; anorexia; and fever, with or without visual symptoms. It is a vasculitis of the middle and large size arteries. The gold standard for diagnosing giant cell arteritis is a positive temporal artery biopsy. Conventional neuroimaging techniques, including MRI and MRA, are usually unrevealing. Color Doppler ultrasound of the superficial temporal artery may demonstrate the "halo sign," stenosis or complete occlusion of the small arterial branches, and the so-called ultrasound "compression sign," suggesting giant cell arteritis [79, 80]. Primary angiitis of the central nervous system may present with periocular pain, especially when the angiitis involves the optic nerve or chiasm [81, 82]. MRI characteristically reveals T2 hyperintense signal and associated fine linear enhancement pattern in the brain parenchyma, frequently along the lenticulostriate vessels, and the optic nerve.

Conclusion

In patients with chronic isolated eye pain and normal neuro-ophthalmic examination, neuroimaging usually does not show an underlying causative lesion. However, early or in low-grade, progressive disease processes, neuroimaging may show a diagnostic, but often subtle, abnormality. Therefore, high index of clinical suspicion and familiarity with neuroimaging findings for secondary ocular pain are necessary. This may preserve vision or even be lifesaving.

Compliance with Ethical Standards

Conflict of Interest   Gabriella Szatmáry declares no conflict of interest.

Human and Animal Rights and Informed Consent   This article does not contain any studies with human or animal subjects performed by any of the authors.

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•• Of major importance

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