Photophobia in a blind patient: an alternate visual pathway

Case report

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✓Photophobia is a common neurological and ophthalmological symptom that has been associated with a growing number of neurosurgical conditions, especially compressive lesions. The exact signaling pathways and neurophysiological features of the disorder are not well understood; however, data from multiple studies have shown the significance of the trigeminal system and the pretectal nuclei in its pathophysiology. The authors report on a rare case of a blind patient who presented with photophobia without evidence of light perception. They also review the literature and early experimental data in an effort to understand the possible neuronal pathways and structures involved in photophobia.

KEY WORDS • photophobia • blindness • signaling pathway • pretectal nuclei • trigeminal pathway

PHOTOPHOBIA, a sensitivity to or an abnormal intolerance of light, is a symptom commonly associated with a variety of ophthalmological, neurological, and neurosurgical disorders. Often, it is associated with anterior segment disease of the eye, meningitis, subarachnoid hemorrhage, head injury, and encephalitis. Patients with intracranial pathophysiologies may suffer from photophobia because of acute meningeal irritation,[16,36] and the sensitivity has also been reported in patients with tumors (pituitary adenomas and craniopharyngiomas) in the region of the optic chiasm.[14] Although not completely understood, photophobia's mechanism of action is thought to involve the trigeminal pathway with possible input from the pretectal nuclei, occipital lobe, and thalamus. In this report, we describe a blind patient with a history of pituitary adenoma and apoplexy who suffered from photophobia. We also review the literature for a possible alternate visual pathway that would mediate the photic signal that may induce photophobia in blind patients.

Case Report

History. This 68-year-old woman with a 20-year history of pituitary adenoma presented to her primary care physician with photophobia and worsening headache. She had been initially diagnosed with pituitary adenoma in 1985 and subsequently underwent five resections involving transsphenoidal and transcranial approaches and resulting in subtotal removal of the tumor. She also underwent fractionated radiation therapy for the adenoma. Subsequently, she lost her vision and received hormonal therapy for panhypopituitarism. Magnetic resonance images obtained on her presentation revealed lateral progression of the pituitary tumor, extending to the right temporal lobe and invading the cavernous sinus on the right (Fig. 1). She was referred to us for further care and management.

Examination. On physical examination, the patient had no light perception in either eye; however, she reported discomfort in her eyes with exposure to light. The discomfort was so severe that the room lights had to be turned off and the windows covered. The patient's pupils were 9 mm and nonreactive bilaterally. Her extraocular motions were difficult to elicit, but she had obvious misalignment and disconjugate gaze. She had an intact corneal reflex in the left eye and right-sided ptosis. Results of funduscopic examination showed a pale and flat optic disk with significant atrophy bilaterally.

Treatment and Posttreatment Course. After therapeutic options were reviewed both with the patient and the multidisciplinary pituitary team, the patient was offered and treated with repeated fractionated radiation therapy; she did not wish to undergo repeated surgery. One week later, she suffered an extensive pontine stroke and died of respiratory failure.

Discussion

Causes of Photophobia

Photophobia can be caused by a variety of disorders, and its origins can range from fairly mild sources, such as post–alcohol ingestion hangover and migraine[8,9] or common eye disease, to even more severe and potentially fatal conditions, such as meningitis or subarachnoid hemorrhage. Anterior segment disorders of the eye, including uveitis, cyclitis, iritis, and blepharitis,[17] are its most common causes. In fact, Lebensohn[17] found that the more superficial the corneal lesion, the more severe the photophobia. However, intracranial pathological entities that involve the meninges,
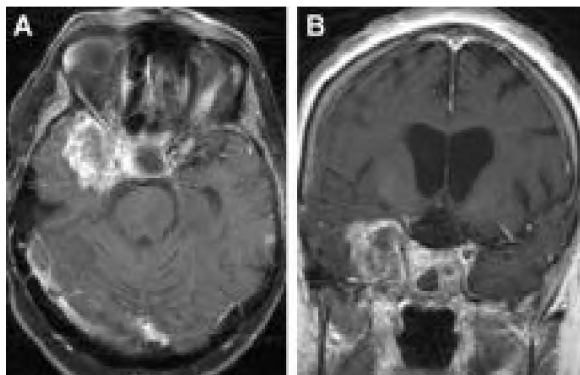
FIG. 1. Axial (A) and coronal (B) magnetic resonance images with contrast demonstrating a heterogeneously enhancing mass in the sellar and right parasellar regions, extending into the right cavernous sinus and right medial temporal lobe and encasing the right cavernous carotid artery.

such as meningitis, intracranial tumors, and pituitary apoplexy, also have been described as possible causes of photophobia.[14] These pathophysiologies are presumed to cause irritation of the basal meninges around the diaphragma sellae[30] and thus lead to photophobia.

Role of the Trigeminal Nerve in Photophobia

In many eye conditions, the mechanism of photophobia is thought to be a feeling of discomfort generated by irritation of the rich innervation to the eye supplied by the first division of the trigeminal nerve. Welch[35] proposed that the trigeminal nerve connections to the midbrain and thalamus might also be involved in the pathophysiology of photophobia in migraine.

Although the neurophysiological aspects of photophobia are poorly understood, the condition does appear to have a central nervous system component as well.[28] The most likely anatomical localization of photophobia is at the site where the visual and pain pathways converge. The signaling pathway for photophobia seems to be anatomically and functionally different from the neural pathway associated with vision. Initially, it was thought that functioning optic and trigeminal nerves were needed for photophobia.[17] However, by demonstrating the presence of light sensitivity in patients with a damaged optic nerve, Custer and Reistad[7] showed that a functioning optic nerve is unnecessary for photophobia symptoms.

Nonetheless, trigeminal innervation of the eye and brain does play an important role in photophobia. Lebensohn[17] showed that an intact trigeminal nerve is necessary to experience the disorder. Eckhardt and colleagues[9] showed that direct irritation to the trigeminal afferents of the eye surface (cornea and iris) can produce photophobia when those structures are exposed to light. They concluded that surface sensitivity must be present for the disorder to occur. Moreover, direct irritation to a nonocular portion of the ophthalmic branch of the trigeminal nerve can also induce photophobia. These authors injected sodium chloride into the frontalis muscle above the supraorbital margin and concluded that irritation of the trigeminal nerve—anywhere along its course or its ophthalmic division—can produce increased light sensitivity.

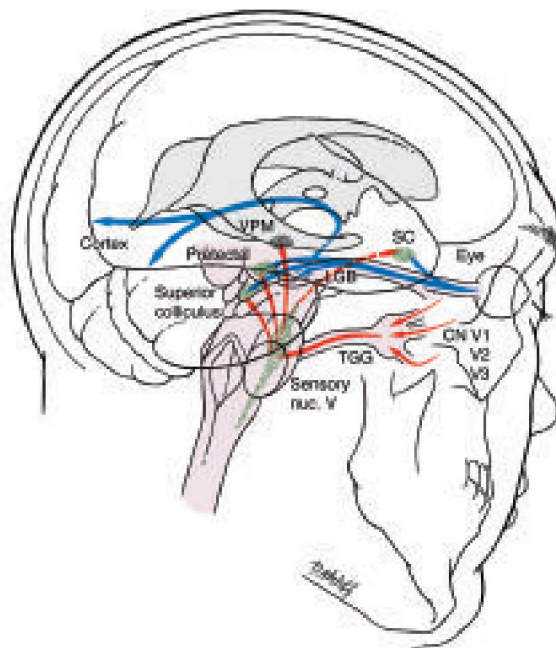The ciliary nerves provide sensation to all layers of the

FIG. 2. Schematic representation of the optic pathway (*blue arrows*) and hypersensitized trigeminal system (*red arrows*), illustrating the role of each in photophobia. Irritation of any of the V1, V2, or V3 branches of the trigeminal system can hypersensitize the whole trigeminal system. CN = cranial nerve; LGB = lateral geniculate body; nuc. V = nucleus five; SC = suprachiasmatic nucleus; TGG = trigeminal ganglion; VPM = ventral posteromedial nucleus.

cornea, uvea, sclera, and conjunctiva, which then join the ophthalmic division of the trigeminal nerve.[25,26,38] This ophthalmic division also provides innervation to the forehead, lacrimal gland, and dura mater of the frontal and middle cranial fossa via the tentorial nerve of Arnold.[25,38] Furthermore, the ophthalmic division also supplies the intracranial portion of the internal carotid artery and middle cerebral artery.[25,26,38] This vast innervation of the meninges may explain the light sensitivity associated with meningitis and subarachnoid hemorrhage.

Role of Pretectal Nuclei in Photophobia

The ophthalmic branch travels with the other branches of the trigeminal nerve to the brainstem through the gasserian ganglion.[25,38] The trigeminal nuclei include the motor nucleus, which serves the motor portion of the trigeminal complex (mainly the mandibular nerve); the mesencephalic nucleus, which serves proprioception of the muscles of mastication; and the trigeminal sensory nuclear complex, which is made up of the main sensory nucleus, nucleus of the spinal tract, nucleus oralis, nucleus interpolaris, and nucleus pars caudalis, which extends into the upper cervical cord.[37,38] The trigeminal nuclei connect with the tegmentum and motor and sensory nuclei in the brainstem (ocular motor nuclei, facial, glossopharyngeal, vagal, hypoglossal, and vestibular nuclei) as well as with the thalamus.[18,27,37] Interestingly, trigeminal nuclei cells connect to the superior colliculus, cerebellum, and deep nuclei as well.[27,37] Specifically, it has been shown that the spinal trigeminal subnucleus in rats has axonal projections to the thalamus, the deep layers of the superior colliculus, the ventral part of the zona

incerta, and the anterior pretectal nucleus.[34] These connections indicate that the trigeminal system is integrally related to many brain processes and reflexes.

An early observation by Eckhardt and colleagues[9] provided some evidence that pretectal nuclei are involved in photophobia. These authors demonstrated that an absent photophobia response in Argyll Robertson pupils is caused by dysfunction of the pretectal nuclei, which enabled them to localize the light sensitivity to the pretectal nuclei. They proposed that photophobia is similar to referred pain involving the optic nerve and the mesencephalic root and nucleus of the trigeminal system because of its close connections to the optic fibers via the pretectal nuclei and the superior colliculus.

The visual pathway provides information regarding both light and color. It is well known that visual information is carried in two parallel visual pathways: the parvocellular (midget ganglion cells) and the magnocellular (parasol ganglion cells) pathways.[3,4,11] Livingstone and Hubel[19] and Croner and Kaplan[6] showed that the parvocellular pathway is involved in processing color and high spatial frequencies, whereas the magnocellular pathway is involved in processing luminance and motion.[11] Magnocellular cells have been shown to be very sensitive to luminance[13] and to respond to changes in contrast.[6] Results of these experiments indicated that photophobia is most likely mediated by the magnocellular visual pathway.

Blink Reflex and Photophobia

It is well known that photophobia is present in blepharospasm, a blinking disorder. The initial symptom in patients with blepharospasm often is photophobia and eye irritation that leads to excessive blinking. The exact afferent pathway for reflexive blinking to light is unknown, although the occipital cortex is thought to have a role because the blink reflex has been found to be normal in patients with a unilateral occipital lobe lesion, absent in those with cortical blindness, and more variable in patients with optic nerve atrophy.[24] Note, however, that data from studies in monkeys have shown that the blink reflex remains intact after bilateral striate cortex removal.[24]

Furthermore, there are multiple reports of a persistent light-induced blink reflex in humans in whom cortical blindness has occurred.[24] In one case report of a man who had suffered a cardiac arrest but maintained an intact light-induced blink reflex despite necrosis of the cerebrum, basal ganglia, hypothalamus, several brainstem nuclei, and superior colliculus, the authors suggested that the afferent pathway might involve the pretectum rather than the superior colliculi.[15] In fact, Itoh and associates[12] reported on a pretectal–facial motor nucleus pathway in cats. Other authors have shown that the destruction of the pretectal nuclei but not the superior colliculus in monkeys can inhibit a light-induced blink reflex pathway.[23] Hence, the visually elicited blink reflexes and perhaps the photophobia pathway travel through the retinotectal projections rather than the occipital pathways, bypassing the visual structures distal to the optic tract and being directed to the facial neurons via the tectum.[12,29]

Possible Afferent Pathways

Data from these experiments provide evidence that there may be two different afferent pathways for photophobia: the trigeminal afferent pathway, which processes the photophobia sensed at the eye level; and the visual afferent pathway, which carries the photic information to the pretectal nuclei where the trigeminal and visual pathways interact (Fig. 2). Local irritation hypersensitizes the eye's local trigeminal nerve endings, thus inducing photophobia directly at the level of the eye (trigeminal afferent pathway). This pathway explains photophobia caused by local eye diseases such as anterior segment disorders (for example, uveitis, cyclitis, iritis, and blepharitis). Irritation of the trigeminal nerve outside of the eye (for example, in the meningeal branch during meningitis) hypersensitizes the entire trigeminal system. In the presence of a hypersensitized trigeminal system, the light signal can induce photophobia at the level of the eye via the trigeminal afferent pathway or the optic nerve pathway; in the latter case, photophobia is induced at the pretectal nuclei where the optic pathway meets the trigeminal pathway (visual afferent pathway).

These last two possible mechanisms explain photophobia caused by the meningeal irritation due to intracranial pathophysiologies. The afferent impulses from light enter the pretectal nuclei through the visual pathway. The spread of the excitation from the site of noxious stimulation in the meninges involves the trigeminal system and nucleus. After spreading throughout the trigeminal nuclei, these noxious afferent impulses exert additional excitatory influence on the pretectal nucleus, inducing photophobia. In addition to the aforementioned pretectal and lateral geniculate body and cortical projections, the afferent impulses from light on the retina enter the suprachiasmatic nuclei as well as the superior colliculi.[5,22] The role of these pathways in photophobia is not known, but future work may reveal their possible function in this disorder.

Photophobia in Blind Patients

In mutated blind mice with near-complete degeneration of rod and cone photoreceptors, most of the nonvision light-regulated functions such as the circadian clock,[10] pupillary light reflex,[20] and photic suppression of melatonin[21] have been retained despite the absence of vision. Recently, Berson, et al.,[2] identified unique inner retinal ganglion cells that function as photoreceptors providing photic information to the brain. These authors specifically showed that these retinal ganglion cells provide nonvisual photic information to the circadian systems. It has also been shown that these nonvision functions are controlled by specific retinal photoreceptors called "cryptochromes" and by melanopsin.[21,31,33] It has been hypothesized that both cryptochromes and melanopsin function as phototransducers in retinal ganglion cells providing photic information to the nonvisual pathways of the brain, including the circadian clock and pupillary light reflex.[32] Perhaps in patients who have no visual photic perception, as in the patient in the present report, the retinal ganglion cells function as photoreceptors providing the photic signal to the hypersensitized trigeminal system. Although the specific site of interaction between the retinal ganglion cells and the trigeminal system is not known, one possible site can lie at the retinal level where the ophthalmic branch of the trigeminal system provides rich afferent enervations of the choroid and blood vessels of the retina.[1]

In neurosurgical patients, photophobia has been reported in patients with meningitis, subarachnoid hemorrhage, traumatic brain injury, pituitary adenoma, apoplexy, cra-

niopharyngioma, and tumors that cause direct irritation of the meninges.[14] In fact, photophobia can be the presenting symptom in patients with pituitary adenoma. In the patient in the present case, photophobia may have been caused by a trigeminal system that had been hypersensitized and then exposed to light stimulation. Although our current hypothesis partially explains the possible mechanism of photophobia, especially in blind patients, further experimental and clinical work is needed to understand more fully its pathophysiology.

Conclusions

Photophobia, a common ophthalmological and neurosurgical symptom, has been associated with various intracranial pathological entities. Although the details of its mechanism of action are not well understood, sufficient evidence supports the significance of the hyperexcitability of the trigeminal system as well as the involvement of the pretectal nucleus in photophobia. In addition, ample evidence indicates that a functional and intact visual pathway is not necessary to experience photophobia. Despite significant efforts to elucidate the neurophysiology of photophobia, further research is needed to shed light on the pathophysiology of this common symptom.

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