Fourth Nerve Paresis and Ipsilateral Relative Afferent Pupillary Defect Without Visual Sensory Disturbance
A Sign of Contralateral Dorsal Midbrain Disease

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We describe a patient with a left trochlear nerve paresis and a left relative afferent pupillary defect despite normal visual acuity, color vision, visual fields, and fundus examination. Magnetic resonance imaging revealed a lesion in the right dorsal midbrain extending from the brachium of the superior colliculus to the inferior colliculus. The anatomy and physiology of the pupillary light reflex are reviewed, as are possible mechanisms for the laterality of afferent pupillary defects with midbrain lesions. The presence of a trochlear nerve paresis with an ipsilateral relative afferent pupillary defect and an otherwise normal ophthalmic exam indicates a lesion in the contralateral dorsocaudal midbrain.

Key Words: Pupil—Trochlear nerve—Afferent pupillary defect—Astrocytoma—Dorsal midbrain—Superior colliculus.

Careful examination of the pupils is an essential part of the ophthalmic evaluation. Pupillary size, shape, and motility should be recorded, and all patients should undergo testing for a relative afferent pupillary defect. The afferent pupillary defect is an extremely sensitive indicator of visual sensory dysfunction, and its presence indicates selective damage to the afferent pupillomotor fibers that project from the retina to the midbrain. While an afferent pupillary defect is typically associated with disease of the retina, optic nerve, or optic tract, it can be seen with unilateral or asymmetric lesions occurring anywhere along the afferent pupillary pathway.

Midbrain lesions can produce an afferent pupillary defect from damage to the afferent pupillomotor fibers traversing the brachium of the superior colliculus. These fibers branch from the optic tract and pass through the brachium of the superior colliculus to reach pretectal pupillomotor nuclei. Pupillary afferent fibers of the brachium of the superior colliculus are not anatomically associated with visual fibers, and lesions in this region produce an afferent pupillary defect without loss of visual acuity or a defect in the visual field.

We report a patient who presented with vertical, binocular diplopia. Neuro-ophthalmologic examination revealed a left trochlear nerve paresis and an ipsilateral afferent pupillary defect unassociated with decreased visual acuity or color vision, or an abnormal visual field. Further evaluation showed an anaplastic glioma infiltrating the brachium of the right superior colliculus and the right side of the dorsal mesencephalon.
A 27-year-old woman developed acute, painless, vertical diplopia. On examination, visual acuity was 20/20 in both eyes at distance and near, and color vision was normal as measured with Hardy-Rand-Rittler pseudoisochromatic plates. Visual fields were full to static and kinetic perimetry. Pupils were 5 mm each. Both pupils reacted to light stimulation, but the reaction of the left pupil was slightly sluggish, and there was a left relative afferent pupillary defect. The patient was orthophoric in primary position at distance and near, but she had a left hypertropia of 8 prism dipters on right gaze. She was orthophoric when her head was tilted to the right shoulder with the face forward, but she developed a left hypertropia of 8 prism dipters when her head was tilted to the left shoulder with the face forward. She also had 3 degrees of excyclotorsion as measured with double Maddox rods. These findings were consistent with a left trochlear nerve paresis. Computed tomographic scanning demonstrated a lesion infiltrating the right side of the dorsal mesencephalon. A craniotomy was performed, and the tumor was subtotally resected. Pathologic examination revealed an anaplastic astrocytoma, and the patient subsequently underwent radiation therapy. Postoperative magnetic resonance imaging showed increased signal in the right midbrain on a T2 weighted image (Fig. 1).

The neural pathway of the pupillary light reflex may functionally be considered a three-neuron arc: Afferent fibers from the retina project to the pretectum; interneurons connect the pretectal nuclei with the Edinger-Westphal nuclei; efferent parasympathetic fibers from the Edinger-Westphal nuclei project to the pupillary sphincter (1). Anatomically, this pathway is actually formed by six neurons: The pathway begins in the retina with a three-neuron relay consisting of photoreceptors, bipolar cells, and retinal ganglion cells (2). Ganglion cell axons travel from the retina through the optic nerve, optic chiasm, and optic tract, and afferent pupillomotor fibers branch from the optic tract and pass through the brachium of the superior colliculus (bypassing the lateral geniculate nucleus) to reach the pretectum. Intercalated neurons connect the pretectum with the pupilloconstrictor motor cells of the Edinger-Westphal nuclei by coursing adjacent to the periaqueductal gray matter. Preganglionic parasympathetic neuronal axons travel via the oculomotor nerve to synapse in the ciliary ganglion, and postganglionic parasympathetic axons travel in the short posterior ciliary nerves to innervate the iris pupillary sphincter muscle. Appropriate pupillary function depends on the integrity of all of these structures, and damage at any point in the circuitry may cause a disturbance of pupillary function.

One such disturbance in pupillary function is the relative afferent pupillary defect. Unilateral or asymmetric lesions of afferent fibers anywhere from the retina to the pretectum can produce a relative afferent pupillary defect, as has been reported with lesions of the retina (3-5), optic nerve (6-9), optic chiasm (3,10,11), optic tract (10-13), and midbrain (14-18).

The proposed pathogenesis for the relative afferent pupillary defect in optic tract lesions is based on the known asymmetry of retinal cell topography and on the asymmetric decussation of nasal and temporal fibers at the chiasm (11,12,13,19). More specifically, the density of photoreceptors is greater in the nasal retina than in the temporal retina (20,21), and retinal ganglion cell axons from the nasal retina decussate in the optic chiasm, while temporal fibers remain uncrossed. There is also asymmetric decussation of retinal ganglion cell axons such that the ratio of crossed to uncrossed fibers is 53:47 (22,23). Optic tract lesions therefore affect more afferent pupillomotor fibers from the contralateral nasal retina than the ipsilat-
eral temporal retina, and an afferent pupillary defect is observed in the contralateral eye (the eye with the temporal visual field defect) (11–13).

While the conventional explanation for an observed afferent pupillary defect with lesions of the optic tract is well accepted, it is possible that additional mechanisms contribute. For example, studies in the cat have demonstrated three types of retinal ganglion cells, designated Y, X, and W. Each cell type has a distinct morphology, conduction velocity, and receptive field property (2,24–30). The largest retinal ganglion cells are Y cells; they project to the superior colliculus and magnocellular layers of the dorsal lateral geniculate nucleus. These Y cells detect movement and gross features of the visual stimulus. The X cells are intermediate in size and project to the parvocellular layers of the dorsal lateral geniculate nucleus. The X ganglion cells function in high resolution vision and are located predominantly at the fovea. The W cells are the smallest retinal ganglion cells. The W cell axons have the slowest conduction velocities and project to the pretectum, superior colliculus, pulvinar, ventral lateral geniculate nucleus and lower layers of the dorsal lateral geniculate nucleus. Recent studies have suggested that a subclass of W cells may provide afferent input for the pupillary light reflex by functioning as luminance detectors and relaying the luminance information to the pretectum (2,29–32). Studies in the cat have also shown W cells to be most numerous in the visual streak nasal to the disc (33,34). Similar studies in primates, including the bush baby, monkey, and human, have also demonstrated a tendency for smaller ganglion cells to reside in the nasal retina (35). If the small ganglion cells of primates are important in luminance detection, as has been suggested for the small ganglion cells of the cat, then the asymmetric distribution of such cells in the human retina may result in more luminance detection in the nasal retina and therefore more afferent input for the pupillary light reflex in the nasal retina.

There is, in fact, evidence in humans that selective illumination of the nasal retina produces a greater direct pupillary response than does equivalent selective temporal retinal stimulation (36).

**FIG. 2.** The anatomy of the pupillary light reflex and the trochlear nerves: The shaded portion indicates a lesion involving the brachium of the right superior colliculus and the right dorsal midbrain, including the right trochlear nucleus and/or fascicle.
This increased pupillomotor sensitivity of the nasal retina, in conjunction with the asymmetric decussation of nasal and temporal fibers at the chiasm, may explain the pathogenesis of the afferent pupillary defect in lesions of the optic tract (36).

Whatever the explanation, the brachium of the superior colliculus contains afferent pupillomotor fibers that have branched from the optic tract to pass toward the pretectum, and one would expect lesions damaging these fibers on either side of the mesencephalon to produce a contralateral relative afferent pupillary defect. This phenomenon has, in fact, been reported (14–18). The pathogenesis of the afferent pupillary defect in this setting is similar to that which occurs with optic tract lesions, but there is no visual field defect, since afferent pupillomotor fibers in the midbrain are not anatomically associated with visual fibers.

Fibers of the trochlear nerve also traverse this region before they decussate. Thus, in a patient with an apparently isolated trochlear nerve paresis, the finding of an ipsilateral relative afferent pupillary defect unassociated with evidence of any retinopathy, optic neuropathy, or homonymous field defect localizes the lesion to the contralateral dorsocaudal midbrain with involvement of the brachium of the superior colliculus (Fig. 2).