

Anisocoria and Middle Cerebral Artery Saccular (Berry) Aneurysm in a Rhesus Macaque (*Macaca mulatta*)

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A 27-year-old female rhesus macaque (*Macaca mulatta*) developed anisocoria. The left pupil was dilated and unresponsive to light. The macaque was euthanized because of unrelated reasons and the body was submitted for necropsy. On gross examination, a berry aneurysm of the right middle cerebral artery causing marked compression of the right optic tract was found. Arteriosclerotic changes were observed microscopically in the right middle cerebral and in the internal carotid arteries. The left iris was markedly degenerated, with atrophy of the constrictor muscle. Compression of the right optic tract may cause homonymous hemianopsia. A dilated and unresponsive left pupil indicated a lesion in the ipsilateral parasympathetic efferent pathway. In the absence of appreciable lesions of the left oculomotor nerve, the most likely cause of mydriasis was the iridic lesion. Intracranial aneurysms are common in humans (2 to 5%), but not in other species. Only about 10% of unruptured aneurysms are associated with neurologic deficits related to mechanical compression, such as visual deficits or anisocoria. Meticulous investigation of the ocular vascular and neural pathways led us to conclude that the anisocoria was unrelated to the aneurysm. To our knowledge, this report represents the first documented case of a naturally occurring intracranial aneurysm in nonhuman primates.

We describe lesions in the central nervous system, intracranial vasculature, and left iris that were related to ocular functional anatomy, ocular reflexes, and vision in a 27-year old female rhesus macaque. The clinical manifestations of each lesion are described and related to the clinical presentation. Anisocoria with mydriasis and loss of pupillary light reflexes (PLRs) in the ipsilateral eye have multiple causes, including central and peripheral nervous system, vascular, and ocular lesions. These two clinical signs are not necessarily overlapping and should be investigated separately. Intracranial aneurysms have been described extensively in humans, but not in other species. Their clinical relevance is mainly due to their propensity for spontaneous rupture, with subarachnoid hemorrhage. However the natural history of unruptured aneurysms is poorly understood, and in many instances, these aneurysms are documented as incidental finding at autopsy. The clinical relevance, etiopathogenesis, and naturally occurring intracranial aneurysms in nonhuman primates (NHPs) will be defined. We further compare the described lesions with similar lesions in humans and contribute to the accumulation of knowledge about intracranial aneurysms in NHPs.

Case Report

A 27-year-old sexually intact female rhesus macaque (*Macaca mulatta*) arrived at our animal facility in September 1999. This macaque was wild caught in February 1975 as a juvenile and was used for breeding purposes. On arrival, the macaque was housed individually in an AAALAC International-approved animal facility, and was managed according to the United States Public Health Service Policy on the Humane Care and Use of Laboratory

Animals. The use of this macaque was approved by the Institutional Animal Care and Use Committee. The macaque was seronegative for *Cercopithecine herpesvirus 1* and was tuberculin skin test negative. On arrival, it was also vaccinated against measles virus (ATTENUVAX, Merck & Co., Inc., West Point, Pa.). This macaque had been naive to experimental work on arrival, and subsequent experimental manipulation was not done.

Anisocoria with mydriasis of the left pupil was noticed in August 2000. The left pupil was dilated and unresponsive to light and lacked direct and consensual PLRs. The right pupil assumed a diameter appropriate to ambient illumination and had normal direct and consensual PLRs (Fig. 1A). On ophthalmic examination, both lenses were slightly opaque; however, the macaque was capable of responding to visual stimuli. For occupational safety and health concerns, the macaque was anesthetized with a combination of ketamine and atropine for all manipulations. Due to sedation, assessment of the visual fields of each eye separately and of the menace reflex were not done.

At the time of presentation, the macaque was also lethargic, anorectic and exhibited abnormal posture characterized by forward extension of the hind limbs. The right hind foot and the right ankle were edematous and warm; the pulse in both hind limbs was strong. The macaque did not manifest neurologic deficits, such as knuckling of the foot (proprioception deficits) or paresis. Supportive care included electrolyte solutions, anti-inflammatory agents, analgesics, and antibiotics. Antibiotics were chosen initially due to suspected cellulitis and/or septic arthritis. Subsequently, antibiotic treatment was indicated to prevent secondary infection from development of decubitus ulcers due to prolonged abnormal posturing. This medical care did not improve the macaque's condition substantially. Due to continued wasting (loss of 21% of body weight) without resuming normal activity in response to medical care, the macaque was euthanized with sodium pentobarbital 24 days from initial onset of clinical signs of disease.

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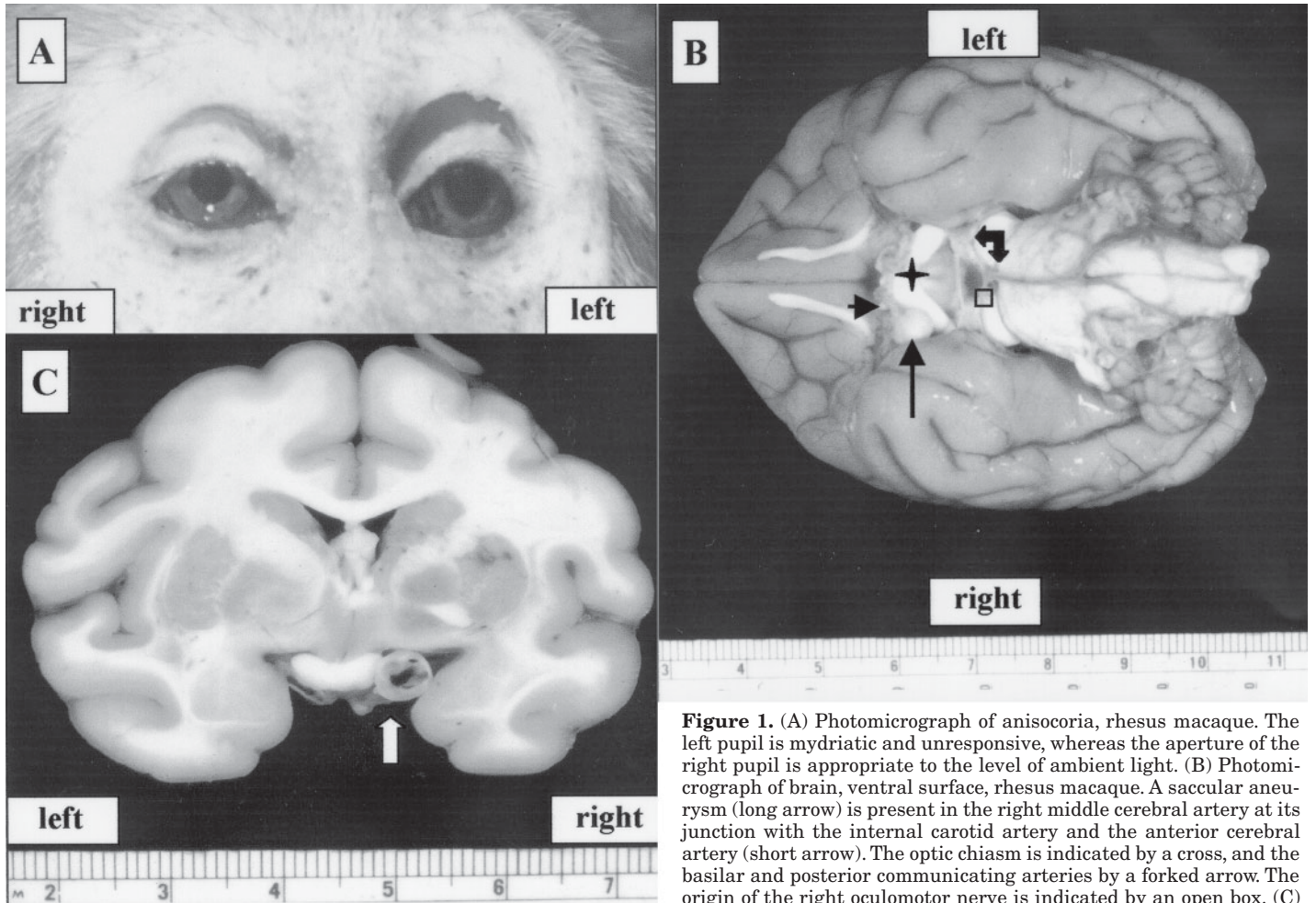


Figure 1. (A) Photomicrograph of anisocoria, rhesus macaque. The left pupil is mydriatic and unresponsive, whereas the aperture of the right pupil is appropriate to the level of ambient light. (B) Photomicrograph of brain, ventral surface, rhesus macaque. A saccular aneurysm (long arrow) is present in the right middle cerebral artery at its junction with the internal carotid artery and the anterior cerebral artery (short arrow). The optic chiasm is indicated by a cross, and the basilar and posterior communicating arteries by a forked arrow. The origin of the right oculomotor nerve is indicated by an open box. (C) Photomicrograph of cross section of the brain, rhesus macaque. A cross section of the midbrain indicates compression of the right optic tract by the aneurysm (long arrow).

Diagnostic tests. Those done during the course of clinical disease included: radiography, clinical pathologic, urine and fecal microbiological, and parasitologic examinations. Abnormalities seen on survey radiographs of the chest, abdomen, and axial appendicular skeleton were: severe osteoarthritis in most tarsal joint articulations and discospondylosis in the thoracolumbar part of the spine, in T10 to L5 vertebrae. Hematologic analysis indicated mild progressive, non-regenerative microcytic anemia and hemoglobinemia (reticulocyte count was not done). This was attributed to chronic disease and partial anorexia. Serum biochemical analytic results were consistent with inflammation, muscle and bone wasting, and/or hepatic disease. Pathogenic bacteria or parasites were not detected by results of urine and fecal microbiological and parasitologic testing. The radiographic findings of multiple chronic arthritic changes and the clinical pathologic findings were consistent with the clinical presentation of lethargy, anorexia, and swollen hind foot as well as the advanced age of this rhesus macaque. However, neither of these findings could explain the anisocoria.

Gross pathologic findings. A saccular aneurysm, approximately 10 mm in diameter, was present in the right middle cerebral artery (MCA) at its junction with the internal carotid artery and the anterior cerebral artery (Fig. 1B and 1C). When the artery was sectioned, it appeared patent proximal and distal

to the aneurysm. The aneurysm compressed the right optic tract immediately caudal to the optic chiasm (Fig. 1B and 1C). The brain appeared grossly normal. Apart from anisocoria with mydriasis of the left pupil, gross abnormalities were not detected in the eyes (Fig. 1A).

Marked bilateral muscular atrophy of the hind limbs was evident, with severe discospondylosis and disk degeneration of the intervertebral articulations from L3- S2. The spinal cord over the lumbosacral junction had moderate dural hemorrhage.

Histopathologic changes. There was marked sectoral degeneration and atrophy of the stroma of the left iris. The superior portion of the iris was characterized by loss of cellularity, particularly in the apical portion of the tissue, with accompanying edema, necrosis, and mineralization. There was complete absence of the constrictor muscle in this region (Fig. 2C and 2D). The inferior portion of the iris had similar, but less advanced lesions, with partial loss of the sphincter, necrosis, and edema of the apical portion of the tissue. A few fibrin strands were attached to the apical region of the iris. The right iris was histologically normal (Fig. 2A and 2B). Both eyes had peripheral retinal atrophy and microcystoid degeneration consistent with aging. Apart from mild posterior subcapsular lens degeneration in the left eye, there were no other ocular abnormalities.

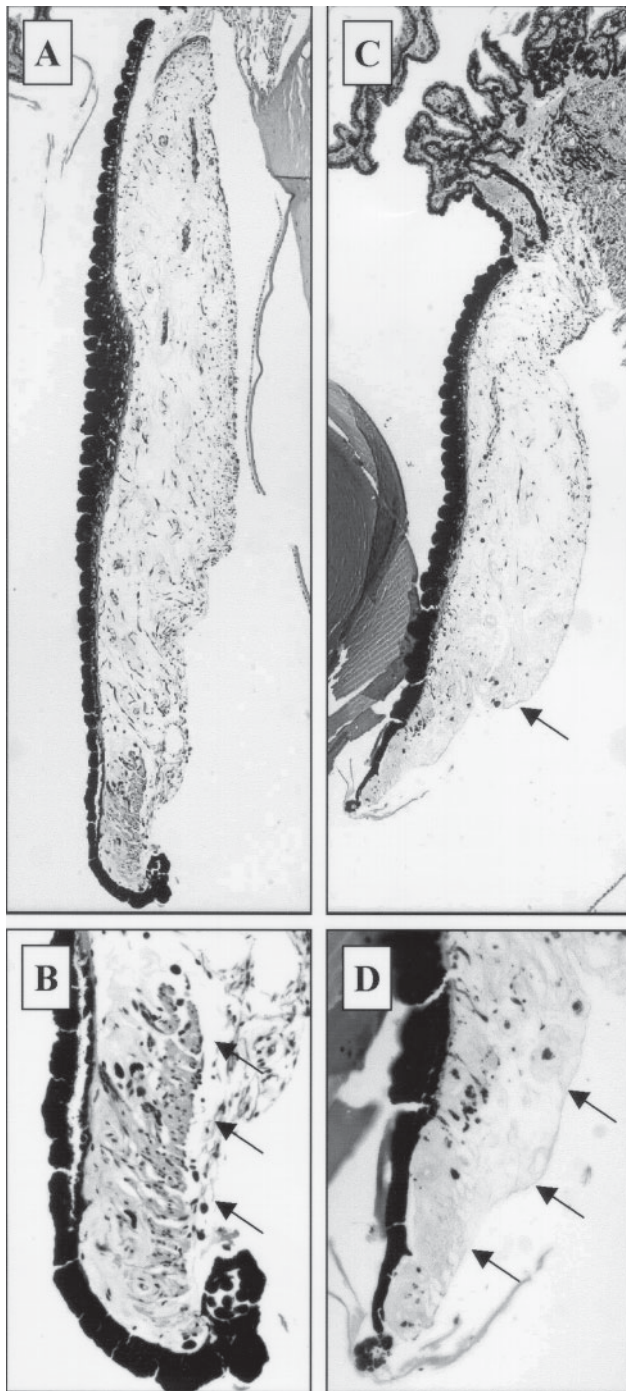


Figure 2. Eyes, rhesus macaque. (A, B) Right eye. The normal constrictor muscle is illustrated in B (arrows). (C, D) Left eye. The left iris has reduced longitudinal length, compared with that of the right. There is severe degeneration of the stroma, with marked loss of cellularity (C), scattered mineralization (arrow), and complete absence of the constrictor muscle (arrows, D), (Hematoxylin and eosin, A and C, magnification 200 \times , B and D, magnification 400 \times).

The wall of the MCA aneurysm was irregularly dilated, with an attenuated tunica media and a markedly expanded adventitia. The adventitia was infiltrated with moderate numbers of mononuclear cells and contained scattered aggregates of fibrohyaline material. There was no evidence of thrombosis. These changes extended proximad along the middle cerebral ar-

tery in all sections examined. The contralateral MCA artery was histologically normal. In addition, there was bilateral arteriosclerosis of the internal carotid arteries. These changes were more severe in the left internal carotid artery, and consisted of marked intimal proliferation and mineralization. Thrombi were not observed in these vessels.

Both oculomotor nerves were dissected from the brain and orbit, and had mild degenerative changes characterized by occasional axonal swelling and Wallerian degeneration. These changes were of similar severity in both nerves. The right optic tract was substantially compressed, with atrophy and consequent increased glial density, compared with the contralateral tract. Histologic abnormalities in the brain were not apparent.

Discussion

The clinical sign of anisocoria may result from either an abnormally dilated pupil (mydriasis) or an abnormally constricted pupil (miosis). In this instance, the macaque had a mydriatic left pupil unresponsive to light. The right pupil assumed a diameter appropriate to ambient illumination and had normal direct and consensual PLRs. The absence of bilateral PLRs makes conditions such as Horner's syndrome, physiologic anisocoria, or sympathetic hyperactivity an unlikely cause for the mydriatic left pupil, and localizes the lesion to the efferent parasympathetic pathway of the left eye (1). The anatomic constituents of this pathway are the left Edinger Westphal nucleus in the midbrain, the pre- and postganglionic parasympathetic fibers of the left oculomotor nerve, and the left iris. In this instance, as the iris of the left eye is markedly degenerate, while that of the right eye is normal, the iris is the most obvious site of a lesion causing mydriasis.

In humans, neuropathy of postganglionic parasympathetic fibers resulting in "tonic pupil" is the most common cause of unilateral mydriasis. This diagnosis is made by use of slit-lamp study and observation of pupillary constriction in response to topical administration of 0.1% pilocarpine (a parasympathomimetic miotic agent) (2). As these procedures were not performed on the macaque, this portion of the efferent pathway was difficult to assess. However, the histologic appearance of the left iris made the likelihood of it responding to pilocarpine a remote possibility. A preganglionic lesion in the oculomotor nerve was unlikely, as histologic changes were mild and bilaterally symmetric. In addition, lesions in this region are typically accompanied by other signs of oculomotor nerve palsy, which were absent in this macaque (2). Similarly, the absence of brain pathologic changes and extrapupillary signs of oculomotor nerve palsy made a mid-brain lesion unlikely. However, very localized midbrain lesions causing pupillary areflexia only have been reported in humans (3), and this possibility is conceivable in this animal, particularly in light of the macaque's vascular disease.

Causes of mydriasis due to iris pathologic changes include glaucoma (1), essential iris atrophy (4), iris atrophy secondary to anterior uveitis (5), or iris ischemia secondary to vascular occlusion (1, 6). Glaucoma is an unlikely cause of mydriasis in this macaque. The typical optic cupping seen in histologic features of glaucomatous eyes was not present. Additionally, evidence of pain, corneal edema, and hyperemia typical of increased intraocular pressure were not detected. Essential iris atrophy can present as unilateral mydriasis, but is typically accompanied by patchy iris atrophy, resulting in irregular appearance of the iris and a distorted pupillary

margin (4). Sectoral iris atrophy is a reported complication of herpesviral infection in humans (5). It is not known whether a similar condition occurs in NHPs, and, in addition, the iris lesions in this animal were not inflammatory. In light of vascular lesions seen in this macaque, ipsilateral circulatory insufficiency of the iris resulting in iris pathologic changes and anisocoria is a realistic hypothesis. Similar to ischemic iris lesions in humans, the iris lesion in this animal was non-inflammatory, degenerative, and most severe toward the pupil, suggesting ischemia originating from an end-arterial system (1, 6). Ischemia of the iris results in sectoral lesions due to the incomplete arterial network of the iris, particularly in the superior temporal region of the iris, closest to the pupil (6). Lesions in this macaque were sectoral and most severe in the superior portion of the iris.

Unilateral mydriasis following general anesthesia and use of parasympatholytic agents in humans has been described (2, 7). In this macaque, pupillary dilatation induced by the anesthesia procedure may have ruptured previously compromised sphincter musculature, resulting in failure of normal PLRs after recovery. The macaque was anesthetized with a combination of ketamine and atropine for all manipulations, and therefore, the pharmacologic effect of atropine, a parasympatholytic agent, should be considered as a contributing factor to the anisocoria.

Another interesting vascular lesion in this macaque was the aneurysm. An aneurysm is a dilatation of a vessel wall, usually an artery. The cavity of the aneurysm is continuous with the lumen of the vessel from which it originates (8). In humans, intracranial saccular aneurysms have great clinical relevance due to their propensity to rupture spontaneously causing subarachnoid hemorrhage, compression injury, and cerebral ischemia from seeding emboli. Extracranial aneurysms in NHPs have been reported (9-11); however, to our knowledge, this report represents the first documented case of naturally occurring intracranial aneurysm in a NHP.

Intracranial arteries are a common location of saccular (berry) or giant aneurysms since the intracranial arteries have thin walls, no external elastic lamina, and no perivascular support. About 85 to 90% of saccular aneurysms in humans are found at arterial bifurcations of the circle of Willis. In this region, the most frequent site is the internal carotid artery, followed by the anterior communicating artery, and the proximal divisions of the MCA (12-16). The prevalence of intracranial saccular aneurysms in humans is 2 to 5%, and MCA is the third most common location for aneurysms. Aneurysms have an age-related onset, and are rarely found in children. The overall prevalence of aneurysms is higher in older women than in older men (12, 17). These epidemiologic data are consistent with this NHP, which was an aged female rhesus monkey with an aneurysm of the MCA. Lack of published data on naturally occurring intracranial aneurysms in NHPs precludes comparative appreciation of the prevalence of the MCA aneurysm in this species.

In humans, intracranial aneurysms represent common lesions that can be visualized by use of angiography magnetic resonance imaging (MRI) and computerized tomography (CT). They are of great clinical relevance because of their propensity to spontaneously rupture (12, 16). Nevertheless, the natural history of unruptured aneurysms is poorly known. Only a minority of cases (about 10%) of unruptured aneurysms, which are mostly giant aneurysms, present various well-recognized focal clinical syndromes related to compression injury (12-14, 18).

The most striking histologic feature of the aneurysm wall is the absence of the muscular tunica media and the internal elastic lamina, both of which end abruptly at the neck of the aneurysm. Apart from the endothelium, the wall of the aneurysmal pouch consists only of fibrous connective tissue of variable thickness (12, 16, 17). These findings are consistent with the described aneurysm in this NHP. Saccular aneurysms vary in size and shape. Their diameter, at necropsy, is usually between 1 and 25 mm. It should be kept in mind that aneurysms tend to shrink after death, and their angiographic registered diameters *in vivo* are at least 30 to 60% greater than values obtained at autopsy or necropsy (12). At necropsy, the aneurysm in this NHP was 10 mm in diameter (Fig. 1B and 1C). Although an *in vivo* cerebral angiography was not performed, it is reasonable to assume that the *in vivo* aneurysm in the macaque was larger than 10 mm since there was marked compression of the right optic tract by it (Fig. 1C).

Aneurysms of the MCA may be associated with clinical signs of disease. Warning signs that were noticed in human patients prior to MCA aneurysm rupture were reported. Among those signs were ocular pain, impaired extra-ocular movement, and localized head pain. In addition, MCA spasm or minor hemorrhage was associated with balance loss, insomnia, visual hallucinations, and general headache (18). Oculomotor nerve palsy may result from aneurysms of the posterior communicating artery or upper end of the basilar artery or giant aneurysms of the internal carotid artery. These aneurysms affect the oculomotor nerve by direct compression and microhemorrhage. Among the clinical signs of oculomotor nerve palsy is ipsilateral dilated fixed pupil (1, 2, 4, 12, 15, 16). Figure 1B indicates the relation between these arteries and the oculomotor nerve. Neither one of these arteries was compressing the oculomotor nerve on either side in this macaque.

The effects of optic tract compression on vision and afferent PLR were considered. When comparing primates with domestic animals, the former have the most developed decussation of the optic nerve axons in the optic chiasm. This is in correlation with binocular field of vision and frontal positioning of the globes. The degree of decussation in primates is slightly > 50%. Unilateral lesions in the optic tract result in visual deficit in the contralateral visual field of each eyeball. This is referred to as hemianopsia. Because the optic tract contains fibers conveying visual input from the ipsilateral nasal hemifield and contralateral temporal hemifield, lesions in the right optic tract result in left homonymous hemianopsia. Although, there are visual field defects, there are no clinical signs of vision loss (19-21). The PLR is controlled by the optic (afferent) and oculomotor (efferent) cranial nerves and their intracranial projections. The afferent and efferent PLR pathways in rhesus macaques were studied. Retinopretectal fibers were found to be the primary afferents involved in the PLR. Once these retinal projections of one eye cross the optic chiasm, they interlace with the fibers that enter both optic tracts and terminate almost symmetrically in either pretectal olivary nucleus. These nuclei are believed to constitute the principal afferent system in PLR. Therefore, afferent PLR is affected by the integrity of the eye, optic disk, optic nerve, or optic chiasm. However, lesions in a single optic tract may cause no PLR abnormality or depressed response in the contralateral eye to the affected optic tract (19, 22). The efferent PLR was found to be intact in this macaque. Evidence of con-

tralateral optic tract lesion may be detected with relative afferent pupillary defects. The relative afferent pupillary defects are detected by a swinging flashlight and observing differences in direct and consensual PLRs in the same eye. (2). Neither the warning signs nor the relative afferent pupillary defects could be accurately appreciated in this macaque. However, such signs may have contributed to the overall presentation of weakness and lethargy in this macaque.

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