Unilateral Light-Near Dissociation in Lesions of the Rostral Midbrain

Examination of the pupillary response to light and accommodation can provide precise information concerning the localization of a lesion within the sympathetic and parasympathetic pathways, the anterior visual pathway, or the brainstem (Table 1). Classical teaching has associated all lesions of the rostral midbrain with bilateral light-near dissociation (LND), defined as attenuation of the pupil light reflex (PLR) with relative sparing of the near response, as one component of Parinaud syndrome. We describe 2 patients with rostral midbrain lesions in whom LND was clinically present only in the eye ipsilateral to the lesion. To our knowledge, this clinical phenomenon has not been previously reported. We provide an explanation for this observation and its implications for our understanding of the anatomy of the pupil light pathway.

Report of Cases. Case 1. A 19-year-old Asian woman had symptoms of headache and diplopia. Oculomotor examination findings demonstrated a vertical gaze palsy with convergence-retraction nystagmus, noncomitant skew deviation, and convergence insufficiency but preservation of all other eye movements. Examination of the pupils revealed moderate anisocoria, with the right pupil being 0.50 mm larger than the left in both bright light and in the dark (Table 2). The light response (LR) and the near response in the left eye were equally brisk and normal; however, in the right eye there was attenuation of the light reflex but preservation of a normal brisk near response (LND). These findings were confirmed by formal measurement of the amplitudes of the LR and near response in each eye, recorded separately under monocular conditions, using infrared video pupillometry. In the left eye both the LR and the near response were normal with no LND (Figure 1A). Slitlamp examination showed no evidence of a tonic pupil (eg, irregular shape, sector palsy, tonic near response, delayed redilation on looking back into the distance) or anterior segment pathologic conditions, nor were there any clinical signs of a third cranial nerve palsy. Her visual acuity and color vision were normal. Magnetic resonance imaging of the brain showed a hyperintense lesion at the level of the rostral midbrain immediately to the right of the aqueduct of Sylvius, within the periaqueductal gray (Figure 2A and B).

Case 2. A 31-year-old man had a sudden-onset headache, vomiting, and poor balance. He reported vertical diplopia and difficulty focusing on near targets. Oculomotor examination findings revealed a noncomitant skew deviation with right hypertropia on right gaze but full horizontal eye movements. Paresis of vertical eye movements and an up-gaze saccadic palsy with convergence-retraction nystagmus was present. Visual acuity and color vision were normal. Examination of the pupils under resting conditions showed a small degree of anisoco-
ria in the dark (the right pupil being larger than the left) that increased in bright light (Table 2). Clinically the right pupil showed an attenuated direct LR compared with that measured in the left pupil, but the near responses were brisk and of normal amplitude in both eyes. As a result, LND was found on the right side but not on the left side (Figure 1B). There were no signs of a tonic pupil or third cranial nerve palsy. A magnetic resonance image of the brain revealed a small hemorrhage secondary to a midbrain arteriovenous malformation on the right side of the aqueduct of Sylvius (Figure 2C). He slowly recovered with a minor residual vertical eye movement deficit.

Comment. The patients described demonstrate the novel finding of unilateral LND in association with some other components of a dorsal midbrain syndrome, namely, supranuclear up-gaze palsy, impaired convergence, and convergence-retraction nystagmus on attempted up gaze. This finding was clinically apparent. We were careful to exclude infranuclear causes of unilateral LND, including various forms of abberant regeneration of the third cranial nerve (eg, miosis associated with attempted abduction, elevation, or depression of the eye), a chronic postganglionic parasympathetic lesion (eg, irregular pupil shape, sector palsy, exaggerated pupil response to an accommodative effort), or local pathologic features within the anterior segment of the eye (eg, uveitis, iritis ischemia, and others), but neither of these cases showed signs of a peripheral lesion. Given the lateralized and rostral location of the midbrain lesions identified by neuroimaging in these cases, it is likely that the asymmetric pupil signs were instead caused by supranuclear disruption to the projections of the pretectal olivary nuclei (PON) to the Edinger-Westphal nuclei (EWN) on only one side, with relative sparing of the PON projections to the other EWN.

Such lateralized dorsal midbrain lesions might also be expected to cause anisocoria. The resting diameter of the ipsilateral pupil should be larger than the contralateral pupil under bright lighting conditions because the light signal cannot reach the ipsilateral EWN from either eye; in the dark, however, when EWN output is not affected by the PON projections, there should be less (or no) anisocoria. Only patient 1 showed the expected increase in anisocoria in the light, with patient 1 showing an insignificant degree of anisocoria under all light conditions. It is hard to interpret this lack of asymmetry in resting pupil size in patient 1. One possibility is that the identified lesion may also be disrupting the central inhibitory projections to the EWN, resulting in relative disinhibition and miosis of the pupil that would counteract any mydriatic effects of removing the excitatory light signal projections from both PON.

Alternatively, it may simply be that any effect of the lesion on anisocoria is being swamped by the many other central influences that affect the tonic output of EWN cells (eg, projections from the locus ceruleus). In contrast, a lateralized and rostrally placed midbrain lesion is not expected to cause asymmetry in the pupillary miosis that accompanies an accommodative effort, yet both patients showed larger amplitude near responses in the ipsilateral eye. Peripheral (postganglionic) lesions are, of course, often characterized by exaggerated near responses, but neither of the near responses in these patients were tonic or exaggerated; therefore, a supranuclear mechanism must be invoked by way of explanation. It is unfortunate that the near responses in both patients were

Table 2. Pupillary Measurements From Both Right and Left Eyes of Patients 1 and 2

<table>
<thead>
<tr>
<th>Patient No.</th>
<th>Eye</th>
<th>Resting Pupil Diameter, mm</th>
<th>Direct Light Response, mm</th>
<th>Near Response, mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initially</td>
<td>R</td>
<td>7.20</td>
<td>6.00</td>
<td>2.60</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>6.70</td>
<td>5.50</td>
<td>1.48</td>
</tr>
<tr>
<td>1 y later</td>
<td>R</td>
<td>7.40</td>
<td>5.35</td>
<td>2.36</td>
</tr>
<tr>
<td></td>
<td>L</td>
<td>7.65</td>
<td>5.52</td>
<td>2.60</td>
</tr>
<tr>
<td>2</td>
<td>R</td>
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</tr>
<tr>
<td></td>
<td>L</td>
<td>5.95</td>
<td>3.15</td>
<td>1.60</td>
</tr>
</tbody>
</table>

Figure 1. Pupillograms recorded from patients 1 (A) and 2 (B) using an infrared pupillometer (series 1800; Whittaker Corporation, Simi Valley, California). (See Fison et al for methods of eliciting and recording the light and near responses). The recordings were made under monocular conditions, with the pupil response being recorded in all cases from the eye that was stimulated (ie, consensual responses were not recorded). Upper traces are of the right eye; lower traces, the left eye. The responses to light (standardized 1 second square-wave pulse under Maxwellian optics) are shown on the left; the responses to an accommodative effort are shown on the right. Scale bars indicate vertical measure of 0.5 mm; horizontal, 2 seconds (A; also B right-hand trace) or 1 second (B, left hand trace).
recorded under monocular conditions (ie, sequentially not simultaneously); as a result, it is possible that bigger near responses were elicited whenever the ipsilateral eye was being tested simply because more accommodative effort was being applied by the patient. In this context it would have been interesting to measure the accommodative range on both sides, but we do not have these data. An alternative explanation might be that the lateralized location of these lesions influenced the symmetry of the near triad (the anatomy of which is still poorly understood).

A summary of the pupil findings expected for lesions placed at different locations within the PLR pathway is given in Table 1 and also shown in Figure 3. We suggest that 3 patterns of pupil abnormality may be found in association with rostral midbrain lesions. We state that anatomical confirmation of many parts of the pupil pathway shown in Figure 3 still do not exist and merely reflects our attempt to logically account for the various clinical observations that are made with lesions in this area. First and most commonly, patients with Parinaud syndrome may show bilateral LND. These patients are usually found to have large extrinsic midline lesions that are thought to compress the posterior commissure and the adjacent PON, effectively abolishing the light response by removing both crossed and uncrossed projections to the EWNs (shown in pink in Figure 3). A severe reduction in the PLR in both eyes, caused by large midline lesions compressing the posterior commissure, is sometimes taken as evidence that most PON projections are contralateral, a clinical inference supported by studies in primates.2-4 However, we know that patients with optic tract lesions show a relatively intact consensual light re-

Figure 2. A, Patient 1. Sagittal T2-weighted brain magnetic resonance image showing a hyperintense lesion at the level of the rostral midbrain. B, Axial section in patient 1 shows that the lesion is located to the right of the aqueduct of Sylvius within the periaqueductal gray. C, Patient 2. Axial T2-weighted brain magnetic resonance image demonstrating a hypointense lesion to the right of the aqueduct of Sylvius within the periaqueductal gray at the level of the rostral midbrain.

Figure 3. Diagram showing the neural circuitry thought to account for the pupillary light reflex (PLR). We state that the pupil pathways illustrated, although not proven anatomically, reflect our attempt to logically account for the various clinical observations that are made with lesions in this area. Lesions of the rostral midbrain may be associated with the following 3 different patterns of disturbance of the PLR: (1) A lesion in the region of the superior brachium (shown in green) that blocks the retino-tectal inputs to one pretemporal olivary nucleus (PON) causes a contralateral relative afferent pupil defect (RAPD) due to asymmetry in the afferent pupillomotor drive from crossed and uncrossed fibers in the optic chiasm. (2) A midline lesion of the posterior commissure, shown in pink, interrupts most projections from both PON, causing bilateral symmetric loss of the PLR with preservation of the near response (bilateral light-near dissociation [LND]). It is suspected that the near-reflex fibers approach the Edinger-Westphal nucleus through the ventral region, unlike the afferent retinal light-reflex fibers that follow a dorsal route. Retinal light-reflex fibers that enter the Edinger-Westphal nucleus dorsally in the rostral midbrain are thought to account for clinical evidence of light-near dissociation in patients with rostral pretectal lesions. (3) A lesion placed more ventrolaterally within the periaqueductal gray, as shown in red, blocks the PON drive to one Edinger-Westphal nucleus; this causes light-near dissociation only in the ipsilateral pupil (unilateral LND) as well as anisocoria in bright lighting conditions.
sponse, suggesting that there must be a route by which PON fibers can convey the light signal to the ipsilateral EWN. We have shown 2 possible routes by which this may be achieved—either there is a double decussation through the posterior commissure (ie, PON output to the ipsilateral EWN is via the contralateral PON) or there is a direct uncrossed projection from the PON to the ipsilateral EWN. There is no anatomical or clinical evidence to distinguish these 2 routes, and so we have shown both by dashed lines in Figure 3.

A second pattern of pupillary deficit is demonstrated by the 2 cases reported herein, namely, that rostral midbrain pathology may cause unilateral LND. This sign is seen if the lesion is placed more ventrally and lateral to the aqueduct of Sylvius (in the region of the periaqueductal gray; shown in red in Figure 3). Finally, a third pattern of pupillary abnormalities may be observed in rare cases if a dorsolateral lesion interrupts the retinotectal inputs to one PON; such lesions (shown in green in Figure 3) give rise to a contralateral relative afferent pupillary defect indicating that more of the afferent pupillomotor drive is derived from crossed than uncrossed fibers at the chiasm. This conclusion is supported both by the physiological evidence (a discreet light stimulus produces a larger PLR when presented to nasal compared with temporal retina) and by the anatomical evidence (crossed fibers outnumber uncrossed fibers in the chiasm with a ratio 53:47) and presumably accounts for the normal phenomenon of contraction anisocoria (the direct PLR is, on average, 6% greater than the consensual PLR).

Conclusion. The cases reported herein together with others reported elsewhere suggest that pretectal lesions may be associated with any of 3 different patterns of pupillary deficit. Midline lesions affecting the posterior commissure cause bilateral LND, lesions located more ventrolaterally within the periaqueductal gray cause ipsilateral LND, whereas lesions located more dorsolaterally within the superior brachium cause a contralateral relative afferent pupillary defect. Careful assessment of the pupil signs in patients with rostral midbrain pathology, paying particular attention to the symmetry between the 2 eyes, may therefore allow more precise localization of the lesion than was hitherto suspected.

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