

Paramedian Thalamopeduncular Infarction: Clinical Syndromes and Magnetic Resonance Imaging

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We prospectively examined 11 patients with magnetic resonance imaging–documented infarction in the paramedian thalamopeduncular region, which is supplied by the superior mesencephalic and posterior thalamo-subthalamic arteries. Variations in the size and rostral–caudal extent of infarction correlated with the following three clinical patterns: (1) With unilateral paramedian mesencephalic infarction, an ipsilateral third nerve paresis was accompanied by mild contralateral hemiparesis or hemiataxia. Contralateral ptosis and impaired upgaze were observed in two patients; one of them showed additional damage to the posterior commissure. (2) With bilateral infarction in the thalamopeduncular junction, involving the mesencephalic reticular formation, supranuclear vertical gaze defects were accompanied by impaired consciousness or memory, and mild aphasia in some patients. Persistent amnesia was observed only when the dominant anterior nucleus or mamillothalamic tract was damaged. (3) With larger thalamopeduncular infarcts, partial or complete third nerve paresis was combined with supranuclear gaze disturbance and delayed contralateral tremor. An unusual gaze disorder, a variant of the vertical “one-and-a-half syndrome,” occurred with a small strategically placed lesion at the thalamopeduncular junction, best explained by selective damage to supranuclear pathways or partial nuclear involvement. The primary cause of these infarctions was embolism to the basilar apex or local atheroma at the origin of the posterior cerebral artery.

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Infarctions in the territory of the basilar artery apex and proximal posterior cerebral arteries generally result in widespread disturbances in neurological function [1]. Impaired ocular motility or vision [2], altered consciousness or behavior [3], and pyramidal or cerebellar dysfunction [4] are often seen in combination after lesions in the upper midbrain and thalamus.

A distinctive feature of paramedian thalamopeduncular infarction is third nerve dysfunction that may be due to nuclear, infranuclear, or supranuclear damage. These structures are compactly located in a volume of a few cubic centimeters [4]. Using high-field magnetic resonance imaging (MRI), detailed anatomical resolution of the upper brainstem and thalamus now provides precise clinical and anatomical correlations.

We have studied 11 patients with ocular motility disorders due to infarction in the rostral midbrain and thalamus as documented by MRI who showed clinical variations that reflected the topography and extent of ischemic damage. These clinical imaging correlations

expand current views of the “classical” brainstem syndromes [5], which have had limited anatomical documentation.

Material and Methods

Study Subjects

Subjects were patients admitted with acute ischemic stroke to the Neurological Institute of New York between August 1986 and February 1990. Patients were included if clinical examination revealed an ocular motility disorder explained by partial or complete third nerve palsy, supranuclear vertical gaze palsy, or both, with MRI studies that showed the acute infarct. Patients were examined in the acute phase by a vascular neurologist (T.K.T., J.P.M.) and separately by a neuro-ophthalmologist (C.D., J.G.O., M.M.B.). Neuropsychological testing was performed in selected patients. Computed tomographic (CT) scan was obtained initially in each patient. Cerebral angiography was performed in four patients.

Complete third nerve dysfunction was diagnosed with unilateral ptosis, limitation of infraduction, supraduction, and adduction, combined with diminished pupillary response to

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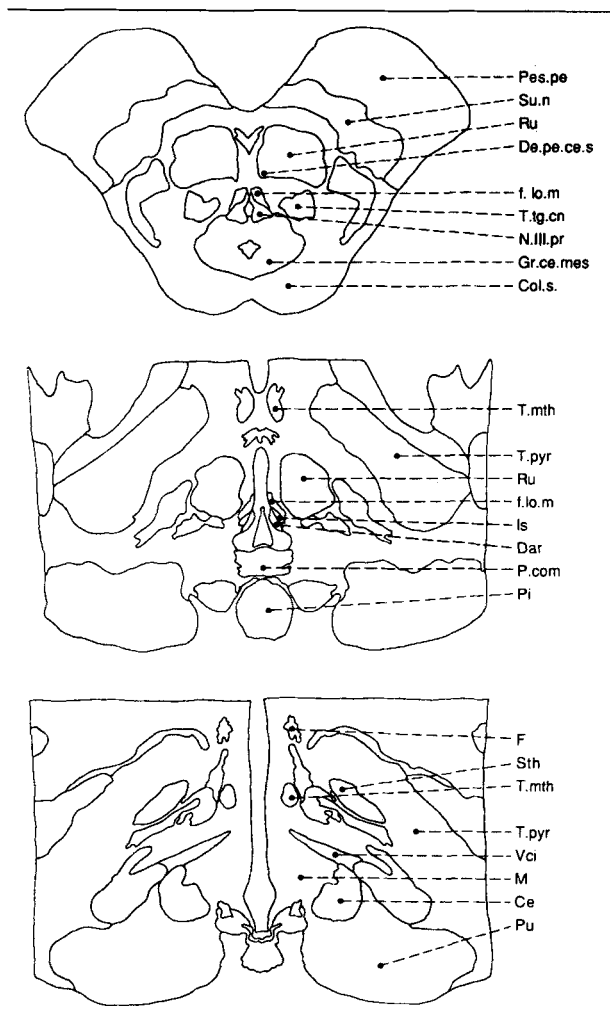


Fig 1. Template adapted from Haines [10] to map the topography of midbrain and thalamic infarcts. Relevant structures are labeled using the terminology of Van Buren and Borke [7] for the thalamic nuclei and Olszewski and Baxter [8] for the midbrain. Level I (top) denotes the upper midbrain level on magnetic resonance imaging (MRI), marked posteriorly (using axial plane terminology) by the superior colliculus (Col.s.) and anteriorly by the terminal portion of the basilar artery within the interpeduncular fossa. This section (5-23 of Haines) includes the caudal-ventral portion of the red nucleus (Ru), oculomotor nucleus complex (N.III.pr) and its fascicle, central mesencephalic gray (Gr.ce.mes), the central tegmental tract (T.tg.cn), medial longitudinal fasciculus (f.lo.m), decussation of the superior cerebellar peduncle (De.pe.ce.s), substantia nigra (Su.n), and a portion of the cerebral peduncle (Pes.pe). Level II (middle) denotes the midbrain-thalamic junction on MRI, marked posteriorly by the splenium of the corpus callosum, the pineal body (Pi), and the posterior commissure (P.com). This section (5-25 of Haines) includes the rostral-dorsal portion of the red nucleus and the mesencephalic reticular formation (MRF) lying rostral and dorsomedial to the red nucleus. The MRF includes several structures involved in the premotor control of vertical eye movements including the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF), the interstitial nucleus of Cajal (Is), the nucleus of Darkschewitsch (Dar), and the nuclei of the posterior commissure (n.pc). Especially critical in vertical gaze is the riMLF, a reticular nuclear group located dorsomedial to the up-

light. A nuclear third nerve lesion was diagnosed with ipsilateral complete third nerve dysfunction and contralateral ptosis with impaired elevation. In the absence of the latter finding, infranuclear damage was inferred. Supranuclear vertical gaze paresis was diagnosed if vertical vestibuloocular reflexes, oculocephalic movements, or Bell's response were preserved, despite defective voluntary saccades or pursuit movements [6]. Patients were classified into the following three clinical subgroups: nuclear or infranuclear third nerve palsy (Group 1), supranuclear vertical gaze palsy (Group 2), and combined nuclear and supranuclear palsy (Group 3).

MRI and Anatomical Analysis

MRI scans were obtained 2 to 17 days after onset of symptoms using a 1.5-T magnet with standard acquisition settings and times to produce T2-weighted images in the axial plane in all patients, and sagittal and coronal views in some patients. With our machine, scanning occurred at an angle of approximately 30 degrees below the axis of the intercommissural axial line, resulting in images that were transverse to the longitudinal axis of the brainstem.

Neuroradiologists (J.A.B., S.K.H.) reviewed MRI scans without clinical information. We used the terminology of Van Buren and Borke [7] for the thalamic nuclei and those of Olszewski and Baxter [8] for the brainstem to identify lesions, following the neuropathological descriptions of paramedian thalamic and midbrain infarcts by Castaigne and colleagues [9]. For anatomical localization, we identified three levels of interest on MRI scans (Fig 1), using the corresponding transverse sections from the atlas of Haines [10]. We also consulted the atlas of Schaltenbrand and Wahren [11] to make visual interpolations using the appropriate axial and sagittal sections. Infarcts were traced on templates designed to match MRI levels and merged by computer to create overlapping topographic maps summarizing the three clinical groups.

Results

Presenting Clinical Features and Vascular Pathology

The five women and six men had a mean age of 65.6 years (range, 38-83 years) (Table 1). Hypertension was present in five patients, and three had diabetes mellitus. The three patients with both of these condi-

per pole of the red nucleus, ventral to Dar, and rostral to IS and the tractus retroflexus [12, 13]. Crossing this zone in the transverse plane is the mamillothalamic bundle (T.mth) of Vicq d'Azyr, which lies ventromedial to the red nucleus, adjacent to pyramidal tracts (T.pyr). In addition, the most ventral portions of parafascicular (Pf) and central nuclei (Ce) of the thalamus are found here. Level III (bottom) or the ventral thalamic level on MRI is marked posteriorly by the splenium of the corpus callosum, and behind it, the parietal-occipital sulcus. This section (5-29 of Haines) includes the dorsomedial or median (M) nucleus, seen dorsally adjacent to the ventricular wall, the upper portions of the central nucleus (Ce) lateral to it, the internal ventrocaudal nucleus (Vci), the pulvinar (Pu) posteriorly, and the anteroprincipal portion (Apr) of the anterior nucleus anteriorly. The columns of the fornix (F) and the subthalamic nucleus (Sth) are also seen on this section.

Table 1. Presenting Clinical Features and Computed Tomographic and Angiogram Findings

Patient No.	Age (yr)/Sex	Vascular Risk Factors			Prior Ischemic Events	Symptoms at Onset	Initial CT Findings (days from onset)	Angiogram Findings
		HTN	DM	Cardiac				
Group 1								
1	83/M	0	0	+ (Angina)	0	Diplopia, ataxia	R midbrain infarct (1)	ND
2	68/M	0	0	0	0	Diplopia, ataxia, perioral numbness	R thalamic and midbrain infarcts (1)	ND
3	58/F	+	+	0	+	Lethargy, L weakness, lid droop	Bioccipital infarcts (3)	Basilar stenosis
4	74/F	+	+	+ (CHF)	+	Lethargy, diplopia, dysarthria	Central midbrain, L thalamic infarcts (1)	Basilar stenosis
Group 2								
5	82/F	0	0	0	0	Stupor, headache, dizziness	Normal (0)	ND
6	55/M	+	0	+ (Angina)	+	LOC, diplopia, R weakness	L thalamic infarct (0)	Vertebral occlusion
7	62/M	0	0	0	0	LOC, L weakness	R thalamic infarct (1)	ND (vertebral occlusion) ^a
8	38/F	0	0	+ (ASD)	0	LOC, vertigo, ptosis	Normal (0)	ND
Group 3								
9	70/M	+	0	0	0	Sudden collapse, aphasia, R weakness	Normal (0)	ND
10	70/F	+	+	0	+	Diplopia, R weakness, lid droop	L midbrain infarct (1)	Basilar and PCA stem stenosis
11	62/M	0	0	0	0	Stupor, L weakness	Bioccipital, thalamic, cerebellar infarcts (0)	ND

^aDiagnosed by Doppler ultrasound.

HTN = hypertension; DM = diabetes mellitus; CT = computed tomographic; 0 = absent; + = present; R = right; ND = not done; L = left; CHF = congestive heart failure; LOC = loss of consciousness; ASD = atrial septal defect; PCA = posterior cerebral artery.

tions (Patients 3, 4, and 10) had severe atherosclerotic disease involving the basilar artery, posterior cerebral artery, or both, as demonstrated by cerebral angiography. They were clinically distinguishable from the other patients by the occurrence of prior transient ischemic attacks (Patients 3 and 4), or stepwise progression of the stroke syndrome (Patients 4 and 10).

Although four patients had cardiac disease (e.g., angina, congestive heart failure), only one had an overt source of cardiogenic embolism, an atrial septal defect diagnosed by "bubble" echocardiography (Patient 8). That patient presented with sudden onset of unheralded stupor and oculomotility disorder, suggesting embolic occlusion of the basilar artery apex. A similar syndrome, clinically indistinguishable, occurred in four others without a demonstrated cardiac source of embolism (Patients 5, 6, 7, and 9). Patients 6 and 7 had recognized extracranial vertebral artery lesions, the presumed source of embolism.

Neurological and Neuroophthalmological Findings

Among Group 1 patients (Table 2), a complete ipsilateral third nerve palsy was combined with contralateral ptosis and elevation defect in Patients 2 and 3. Patient 4 showed bilateral complete oculomotor palsies. Contralateral hemiataxia occurred in two patients, and mild contralateral weakness was evident in three patients.

In Group 2, all four patients had vertical gaze defects, including one (Patient 7) with downgaze impairment alone. Consciousness was altered at the onset of stroke in all four patients, and an amnesic syndrome was prominent in two patients (Patients 7 and 8). One had an anomic aphasia (Patient 6). Minimal unilateral weakness was evident in three patients, but none showed incoordination.

Group 3 patients shared features of patients in both Groups 1 and 2, although pyramidal signs tended to be more severe when present. A unique finding was delayed tremor (Patients 10 and 11), seen only in this group.

MRI Findings and Anatomical Features

In all but one patient (Patient 1), infarction was evident on at least two of the three levels (Table 3). Early CT scanning, most performed within 24 hours, showed the midbrain infarct in four patients; thalamic infarcts were seen in five (see Table 1). Because CT and MRI were obtained at different times after onset, we could not assess the detection sensitivity of the two imaging methods, although MRI provided superior anatomical definition.

In Group 1 (Fig 2), infarction involving the paramedian upper midbrain (level I) was evident in all four and bilateral in one patient. The infarct was confined

Table 2. Neurological and Neuroophthalmological Findings

Patient No.	Impaired Alertness	Impaired Memory	Aphasia	Oculomotor Function		Vertical Gaze		Hemiparesis		Tremor		Ataxia	
				R Third	L Third	Up-gaze Defect	Down-gaze Defect	R Limbs	L Limbs	R Limbs	L Limbs	Limb	Gait
Group 1													
1	0	0	0	Complete; pupil-spared	0	0	0	0	0	0	0	+L	+
2	0	0	0	Complete	Ptosis; SR palsy	NT	0	0	F	0	0	+L	+
3	+	+	0	Complete	Ptosis; SR palsy	NT	0	0	+	0	0	0	0
4	+	0	0	Complete	Complete	NT	NT	+	0	0	0	+R	+
Group 2													
5	+	0	0	0	0	++	++	0	+	0	0	0	0
6	0	+	+	0	0	++	+	+	0	0	0	0	0
7	+	++	0	0	0	0	++	F	0	0	0	0	0
8	+	+	0	0	0	+	++	0	0	0	0	0	0
Group 3													
9	+	0	+	0	Partial (?) IR palsy	R >> L	0	+	0	0	0	0	0
10	0	0	0	0	Complete	+	0	+	0	+	0	+R	+
11	++	NT	NT	Complete	0	+	+	0	++	+	0	+R	NT

R = right; L = left; 0 = absent; Complete third = involvement of lid, pupil, and motility; + = present; SR = superior rectus; NT = not testable; ++ = severe abnormality; F = central facial paresis only; IR = inferior rectus.

Table 3. MRI Findings Identifying Anatomical Areas Involved in Thalamopeduncular Infarction

Patient No.	N.III.pr	III.fsc	De.pe.ce.s	Pes.pe	Ru	MRF	P.com	Thalamic Nuclei			
								Pf	Ce	M	Other
Group 1											
1	+(R)	+(R)	+(R)	0	+(R)	0	0	0	0	0	0
2	+(R)	+(R)	+(R)	0	+(R)	0	0	0	+(R)	+(R)	0
3	0	+(R)	0	+(R)	+(R)	+(R)	+(R)	+(R)	+(R)	+(R)	0
4	+(R, L)	+(R, L)	+(R, L)	+(R, L)	+(R, L)	+(R, L)	0	+(R, L)	0	0	0
Group 2											
5	0	0	0	0	0	+(R > L)	+(R, L)	+(R, L)	+(R)	+(R)	0
6	+(L)	0	+(L)	0	+(L)	+(L)	+(R, L)	+(L)	+(R, L)	+(L)	0
7	0	0	0	+(L)	+(R)	+(R)	+(R)	0	0	0	T.mth (L)
8	0	0	0	0	+(R)	+(R > L)	+(R, L)	+(R > L)	+(R > L)	+(R > L)	Apr (R) T.mth (R)
Group 3											
9	0	0	0	0	+(L)	+(L)	+(L)	+(L)	+(L)	+(L)	0
10	± (L)	+(L)	+(L)	+(L)	+(L)	+(L)	+(L)	+(L)	0	0	0
11	+(R)	+(R)	+(R)	+(R)	+(R)	+(R > L)	+(R, L)	+(R)	+(R)	+(R)	0

MRI = magnetic resonance imaging; N.III.pr = oculomotor nucleus complex; III.fsc = oculomotor fascicle; De.pe.ce.s = decussation of the superior cerebellar peduncle; Pes.pe = portion of cerebral peduncle; Ru = red nucleus; MRF = mesencephalic reticular formation; P.com = posterior commissure; Pf = parafascicular; Ce = central nucleus; M = median; + = infarction present; R = right; 0 = no infarction; L = left; ± = infarction indefinite; T.mth = mamillothalamic bundle in transverse plane; Apr = anteroprecipal.

to the midbrain in Patient 1, including the oculomotor nucleus complex (N.III.pr) and decussation of the superior cerebellar peduncle (de.pe.ce.s), but sparing the cerebral peduncle (Pes.pe). When the peduncle was involved, only the medial portion was affected, explaining the mild weakness. The other three had concomitant thalamic lesions, including two involving the mesencephalic reticular formation (MRF), one unilateral (Patient 3) and the other bilateral (Patient 4). Involvement of the posterior commissure (P.com) occurred in Patient 3 only; she had a contralateral elevation defect in addition to a third nerve palsy.

In Group 2 (see Fig 2), three had bilateral infarcts at the midbrain–thalamic junction (level II), extending to the paramedian thalamic region (level III). One patient showed unilateral damage to the mamillothalamic tract (T.mth) (Patient 7), and another appeared to show involvement of the N.III.pr on level I (Patient 6), despite the absence of clinical signs indicating nuclear or infranuclear dysfunction. Subsequent imaging showed no abnormality at that level, consistent with resolving brain edema.

Group 3 patients showed infarct patterns seen in patients in Groups 1 and 2, but were generally more

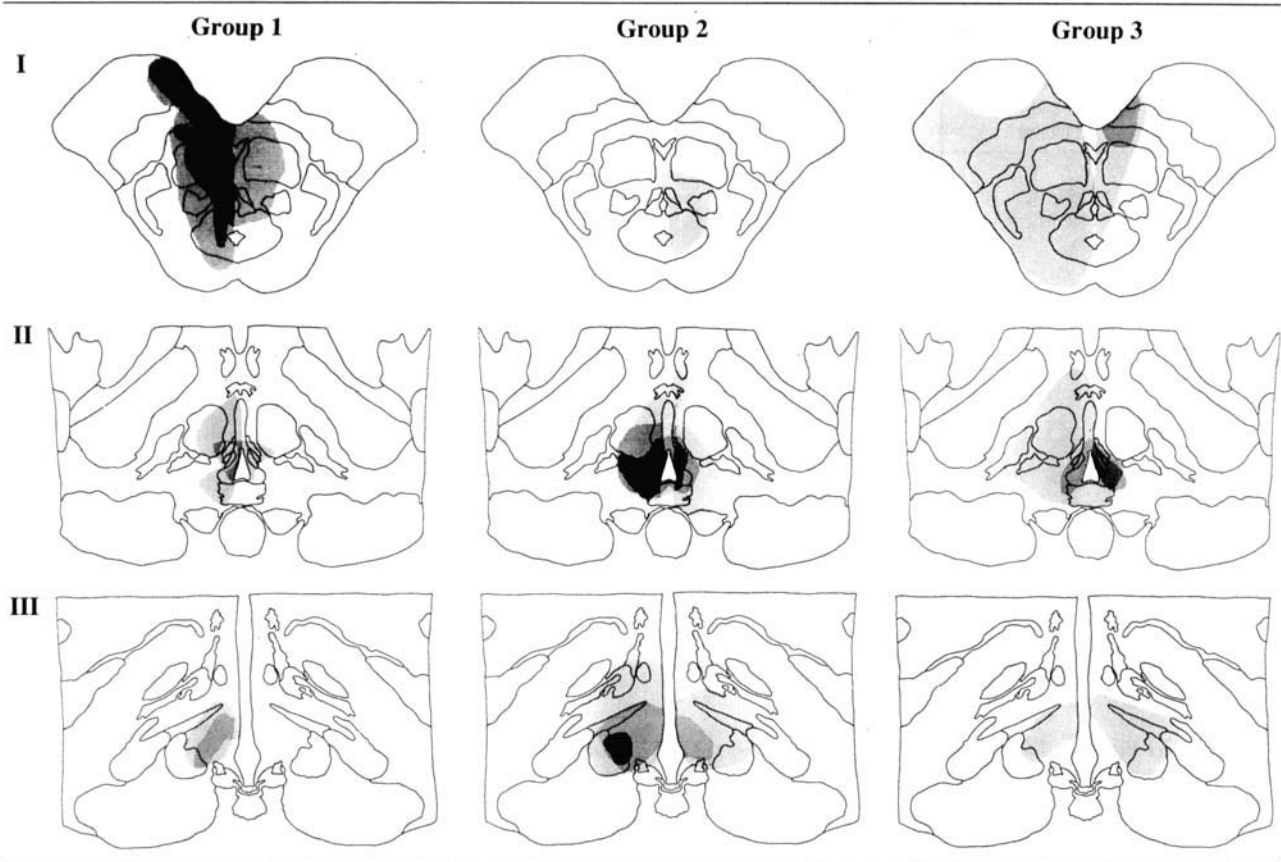


Fig 2. Templates showing infarct topography for 11 patients with thalamopeduncular infarcts. The anatomical levels include level I (upper midbrain), level II (midbrain–thalamic junction), and level III (ventral thalamus), which are illustrated in more detail in Figure 1. The clinical groups are comprised of four patients with nuclear or infranuclear third nerve palsy (Group 1), four patients with supranuclear vertical gaze palsy (Group 2), and three patients with combined nuclear and supranuclear palsies (Group 3). Specific clinical features of the three groups are summarized in Tables 1 and 2. The degree of “shading” indicates the areas most frequently involved by infarction.

extensive (see Fig 2), except for Patient 9 (Fig 3) whose small, but strategically placed infarct was associated with an unusual oculomotility syndrome (see below).

Illustrative Patient Reports

Patient 4 (Group 1)

A 74-year-old woman was admitted with slurred speech, drooping of the right eyelid, and double vision. Four months earlier, she had a transient ischemic attack with multiple small deep infarctions found on CT scan and a normal ophthalmological examination. On examination she was somnolent but arousable, disoriented, and spoke fluently with only slight dysarthria. She performed serial 7's, recalled two of three items after 5 minutes, and showed no language disturbance. There was a minimal right central facial paresis but normal limb strength and tone. Minimal ataxia of the right arm and leg was evident, with a mild terminal intention tremor. Sensation was reduced in both feet to vibration, and on the right side to pinprick. Tendon reflexes were hypoactive bilaterally,

and toes were flexor. She had mild postural instability, falling backward when attempting to walk.

Visual acuity and fields were normal. Bilateral lid ptosis was present, left more than right. The left pupil was 6 mm and fixed to light, but the right pupil was 3.5 mm and reactive. On horizontal gaze, adduction of the left eye was impaired, with abducting nystagmus in the right eye. Abduction was full bilaterally. Upgaze was limited to a 1 to 2-mm excursion and downgaze was moderately restricted, more in the left eye. Convergence was absent. Two days later, ptosis on the right became complete, the pupil became fixed at 6.5 mm, and vertical gaze was absent. Consciousness and motor signs did not change.

Brain CT scan on admission suggested early infarction in the central midbrain and left medial thalamus. MRI scan obtained 10 days after stroke onset revealed bilateral infarctions of the paramedian upper midbrain with minimal involvement of MRF and parafascicular nuclei of the thalamus (Pf) (see Fig 3). Left vertebral angiography showed mild irregularity of the midbasilar region and slight narrowing of the posterior cerebral artery (PCA) stems bilaterally. The stroke mechanism was presumed due to nonstenosing local atheroma of the proximal PCA and distal basilar arteries, leading to occlusion of thalamopeduncular penetrator(s).

Patient 7 (Group 2)

A 62-year-old man with a left ocular prosthesis for trauma 20 years ago, suddenly lost consciousness. He awoke within seconds, but had two additional episodes of stupor. On examination the following day, consciousness fluctuated from a

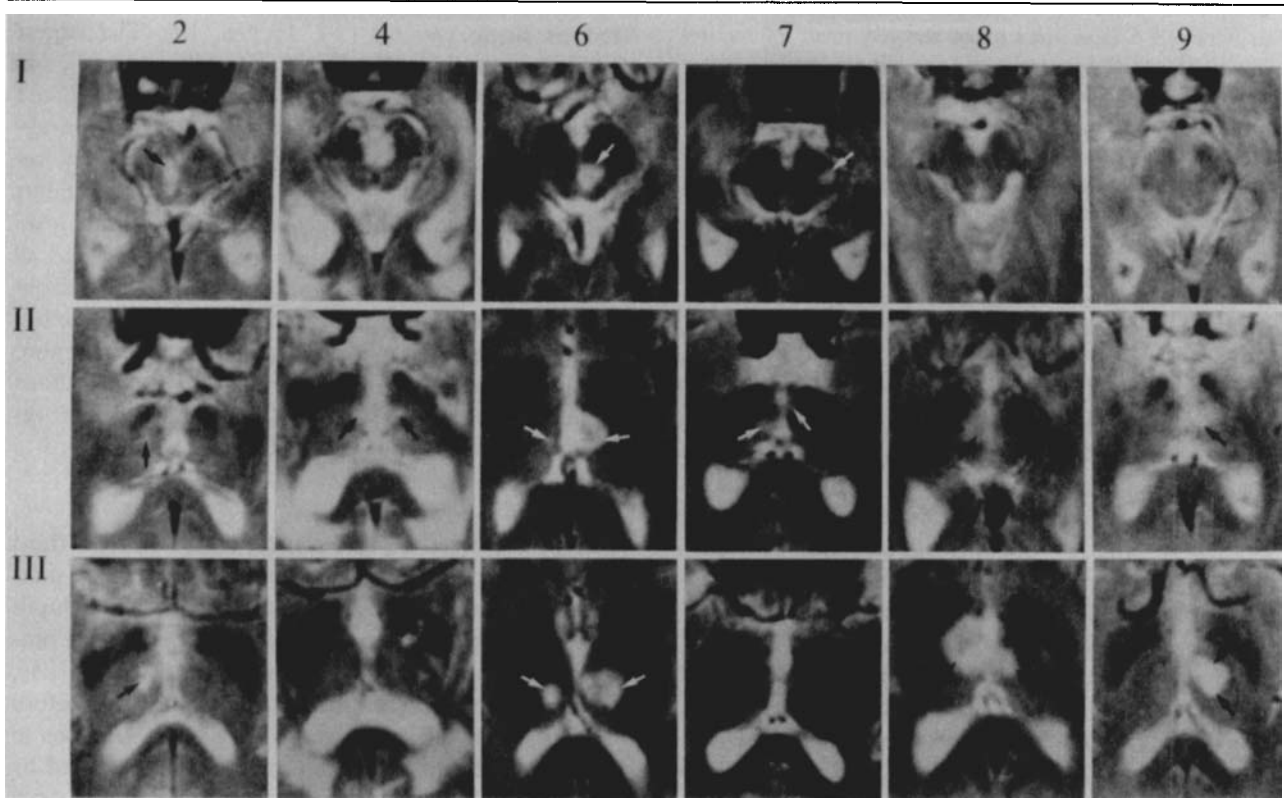


Fig 3. T2-weighted magnetic resonance imaging scans in the axial plane of selected patients (Patients 2, 4, 6, 7, 8, and 9) shown at the three anatomical levels illustrated in Figure 1. Arrows indicate the relevant lesions, which are identified in Table 3. Clinical features are described in the text and in Tables 1 and 2.

deep sleep-like state to normal alertness. When fully alert, he spoke softly but clearly, appeared placid and unconcerned, and showed a severe anterograde and retrograde amnesia. He gave erroneous or confabulatory responses to questions about his age, date of birth, home address, telephone number, current date and location, and the President. He registered but failed to recall items. A mild left central facial paresis was evident without limb weakness, incoordination, or sensory impairment, except for a stocking distribution loss to pinprick. Tendon reflexes were normal. Gait was not tested.

Visual acuity, fields, and the pupil were normal in the right eye. Horizontal gaze was full, including opticokinetic response. Upgaze was slowed but full. Downgaze saccadic movement was absent past the midline, but full to pursuit and present with vertical Doll's maneuver. Vertical opticokinetic nystagmus was absent in both directions. Electromyogram testing of the left eye demonstrated normal inhibition of the superior rectus but no activation of the inferior rectus on attempted downward saccade. The amnesic state persisted for weeks, whereas the downgaze defect improved to near normal by the 13th day when MRI scan was obtained.

Brain CT scan 1 day after onset of symptoms showed a right paramedian thalamic infarction. MRI scan revealed bilateral, asymmetrical infarctions involving the MRF and P.com on the right, and mamillothalamic tract on the left

(see Fig 3). A small, laterally placed, discontinuous (likely unrelated) infarction in the left cerebral peduncle was also seen. Doppler examination of the vertebral arteries showed high resistance flow on the right, consistent with occlusion. Transcranial Doppler of the basilar artery was normal. Cardiac studies showed no source of embolism. Electroencephalogram (EEG) showed intermittent generalized bursts of rhythmic delta activity, maximal over the right frontal-temporal regions. The stroke mechanism was presumed to be embolism to the basilar apex related to vertebral artery atherosclerosis.

Patient 9 (Group 3)

A 70-year-old man complained of occipital headache and dimming of vision, followed by right-sided weakness, causing him to fall. On examination, he was somnolent, dysarthric, and slightly dysnomnic with rare paraphasic errors in spontaneous speech. Comprehension of spoken words was slightly impaired, and he was unable to read. Repetition and verbal memory were normal. He had a mild right central facial and lingual paresis with weakness of the right shoulder. Coordination of the limbs, sensation, and reflexes were normal. Gait, tested the next day, was normal. Language improved to a mild dysnomnic dysphasia over the next 2 days.

Visual acuity, fields, fundi, pupils, and lids were normal. A prominent right hypotropia in primary position was present. Upgaze was severely limited on the right, not passing the midline, and minimally impaired on the left. Upward saccades were slow, and upgaze-evoked nystagmus was evident bilaterally (OS > OD). Downgaze was moderately restricted in the left eye, but normal in the right eye. Horizontal saccades were full but slow bilaterally.

Brain CT scan the day of symptom onset was normal. MRI scan obtained 5 days after onset showed small infarctions involving the MRF bilaterally and the left paramedian thalamus (see Fig 3). Echocardiography and Holter monitor demonstrated no cardiogenic source of embolism. EEG showed mild diffuse slowing. Cerebral angiography revealed no abnormalities of the vertebral artery, but minimal irregularities in the distal basilar and PCA stems bilaterally, left more than right, consistent with either local atheroma or recanalizing embolism. The stroke mechanism was presumed to be embolism to the top of the basilar artery, although no obvious source was identified.

Discussion

The findings in these 11 patients justify the concept of a paramedian thalamopeduncular syndrome. The essential feature is clinical evidence of third nerve dysfunction (whether nuclear, infranuclear, or supranuclear) combined with motor effects (hemiparesis, ataxia, or movement disorder) and altered mental function (consciousness, memory, or language).

The infarct topography demonstrated by MRI scanning illustrates the "heart" of the territory supplied by paramedian thalamopeduncular arteries as defined by Castaigne and colleagues [9]. The area includes the mesencephalic gray matter, third nerve nucleus and its fascicle, intralaminar and parafascicular nuclei, inferior *internal region* of the median nucleus, and medial anterior region of the central nucleus. Less consistently involved are the superior cerebellar peduncle and decussation, and the medial third of the cerebral peduncle. To this list, we add the MRF, important in the supranuclear control of vertical gaze [12, 13].

The territory supplied by the thalamopeduncular arteries can be considered a unitary anatomical–functional region. Clinical variations reflect the rostral–caudal extent of infarction of the upper midbrain and thalamus [14, 15], and whether damage is unilateral or bilateral [3], topographical effects that relate to vascular supply. As reviewed by Castaigne and colleagues [9], the superior mesencephalic arteries (also known as the paramedian peduncular arteries) irrigate the paramedian portions of the upper midbrain. This supply can be distinguished from the paramedian thalamic arteries, also known as the posterior internal optic arteries, retromamillary thalamoperforating pedicle, the posterior thalamosubthalamic arteries, or the deep interpeduncular profunda artery. However, the mesencephalic and paramedian thalamic arteries commonly arise together as a single pedicle from the proximal stem of the PCA, which Percheron [16, 17] has termed the basilar communicating artery. Because they supply neighboring territories, infarcts in the paramedian midbrain and thalamus often occur in combination rather than in isolation [9], as seen in 10 of our 11 patients.

Most previous studies of thalamopeduncular infarcts

relied on pathological or brain imaging findings in a few or single patients [14, 15, 18, 19]. The largest series, reported by Castaigne and colleagues [9], has served as the pathological benchmark, but it was based on retrospective review. In our prospective clinical–MRI correlation, analysis of infarct topography revealed a concentration of damage at level I for patients with the nuclear or infranuclear third syndrome, level II for those with supranuclear gaze disorders, and all three levels in combined syndromes. Some of our observations corroborated those previously reported, but additional findings indicated variations on the more commonly understood clinical–anatomical correlations or illustrated less well-defined anatomical points related to associated neurological signs.

Oculomotility Syndromes

Patient 1 showed a pupil-sparing complete right third nerve palsy combined with left-sided hemiataxia, similar to the syndrome described by Claude [20]. Pupillary reactivity may be preserved, despite complete ptosis, even with *fascicular* damage intraaxially [21], because of spreading of the third nerve fascicles before converging at the interpeduncular fossa. Variations in the *nuclear* third nerve syndrome were represented by Patients 2 and 3 who showed ipsilateral third nerve palsy combined with a contralateral ptosis as well as impaired elevation from superior rectus paresis, implying selective damage to the subnuclei of the oculomotor complex [22–25]. The studies of Warwick [26], based on rhesus monkeys, indicated that the subnucleus of the superior rectus component is located medially and has crossed projections, serving the contralateral muscle. A unilateral paramedian lesion here may thus cause an ipsilateral third nerve paresis combined with contralateral superior rectus impairment. Bilateral ptosis is often seen because the levator palpebrae superioris muscles are served by a single midline nucleus at the caudal end of the complex. Bilateral ptosis in isolation may be a mesencephalic infarct sign [27]. However, nuclear damage may not be the sole explanation for a contralateral elevation defect because impaired upgaze could result from a concomitant lesion of the posterior commissure, seen in Patient 3.

Bilateral third nerve palsies in relative isolation may also result from bilateral paramedian lesions, as seen in Patient 4, who showed only minimal atheroma of the basilar communicating artery. These findings resembled an autopsied patient [28] who had bilateral ophthalmoplegia and a similar infarct topography. Such circumscribed effects are possible from limited occlusive disease, resulting from variations in the vascular supply [16], including the occurrence of a single pedicle from the basilar communicating artery on one side bifurcating to irrigate the thalamopeduncular regions bilaterally.

Supranuclear gaze palsy may result from more ros-

trally placed infarctions in the MRF, a premotor relay station for saccades in the vertical plane, comparable in function with the pontine reticular formation mediating horizontal eye movements [13]. Damage to the MRF, usually bilateral, causes downward, upward, or combined vertical gaze palsies, as observed in all four patients in Group 2. Paralysis of downgaze has been associated with lesions of the riMLF in monkeys [29] and in humans [12]. Among autopsied examples of selective downgaze palsy from infarction, involvement of the rostral interstitial nucleus of the medial longitudinal fasciculus (riMLF) has been bilateral in all, although there has been uncertainty about the rostral-caudal extent necessary for clinical effects, as exemplified by the patient [30] with lesions of the red nucleus around the tractus retroflexus on the right (just caudal to riMLF) and nucleus of Darkschewitsch on the left. Similarly, Patient 7 showed MRF involvement on the right and a lesion ventromedial to the red nucleus on the left.

Paralysis of upward gaze, or Parinaud's syndrome [31], arises from bilateral lesions of the fibers and nuclei of the posterior commissure [32], or from a large unilateral lesion whose functional effect is bilateral because it involves crossing upgaze efferents from the riMLF and the interstitial nucleus of Cajal [13]. These large unilateral lesions may also cause combined upward and downward gaze palsies. After reviewing autopsied patients with vertical gaze palsy, Buttner-Ennever and co-workers [12] concluded that the "common lesioned area" leading to isolated paralysis of upgaze is caudal and ventral to lesions causing isolated paralysis of downgaze. The sagittal images in two patients with combined palsies support that view (Fig 4); in Patient 6, upgaze was more affected than downgaze, and the infarct was larger and more caudally placed than the infarct in Patient 8, who had a more severe disorder of downgaze. Patient 5 had equal restriction of upgaze and downgaze with bilateral, small lesions of the MRF including the white matter pathways adjacent to the posterior commissure on both sides. Both Patients 5 and 6 showed loss of voluntary vertical eye movements, as well as impaired vestibuloocular reflex movements in the acute phase, with recovery in a few days, as seen in other examples of "supranuclear" palsy [19, 33–36]. It is therefore necessary to distinguish between acute and subacute disturbances; otherwise, anatomical inferences may be faulty.

We also identified a third group of patients with combined *nuclear and supranuclear disorders*, the expected findings from extensive thalamopeduncular destruction [37]. Patient 11 had the largest infarction resulting in a complete third nerve palsy with supranuclear vertical and horizontal gaze palsies. Larger peduncular infarcts have been associated with gaze palsy in the horizontal plane, explained by interruption of the descending corticopontine pathways [38].

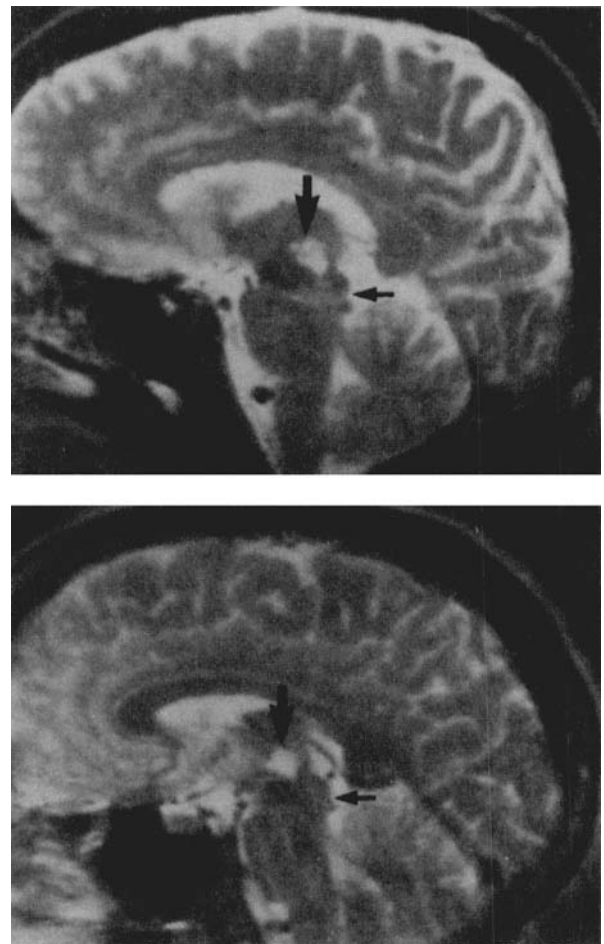


Fig 4. T2-weighted magnetic resonance imaging scans in the sagittal plane of Patient 6 (top) who showed impaired upgaze more than downgaze, compared with Patient 8 (bottom) who showed impaired downgaze more than upgaze. Using the superior colliculi (small arrow) as a reference, the infarct (large arrow) in Patient 6 appears larger and more caudally placed than that in Patient 8.

Strategically placed, smaller lesions may produce unusual syndromes that may result from supranuclear (including selective "prenuclear") or partial nuclear damage [39, 40]. In Patient 9, the major signs were downgaze impairment in the left eye and a bilateral upgaze defect mainly involving the right eye without impairment of horizontal gaze, pupillary function, or eyelids. On MRI scan, the infarct affected the region of the riMLF and posterior commissure on the left, all just rostral to the third nerve nucleus. The clinical findings may be explained by damage to the descending pathways for downgaze from the riMLF at or below the level of decussation just before reaching the third nerve, especially affecting fibers innervating the ipsilateral inferior rectus. Partial nuclear damage is another possibility, but was not evident on MRI scanning. In addition, involvement of prenuclear fibers from the posterior commissure to the ipsilateral (left) sub-

nucleus of the contralateral superior rectus could explain the prominent right-sided elevation palsy [39]. Our patient might be considered to have a variation of the vertical "one-and-a-half" syndrome from unilateral paramedian thalamopeduncular infarct described by Bogousslavsky and Regli [40] whose patient showed an ipsilateral monocular paresis of downgaze combined with bilateral symmetrical upgaze defect.

Pyramidal and Extrapyramidal Syndromes

Motor effects are commonly found with paramedian midbrain infarcts, but in our patients, they were relatively mild, consisting of slight hemiataxia or minimal weakness. Claude and Loyez [41] attributed the contralateral hemiataxia and asynergia to lesions of the red nucleus or decussation of the superior cerebellar peduncle. Our patients suggest that damage to the decussation was more likely because both structures were affected in Patient 1, who had the typical Claude's syndrome [20] with ipsilateral third paresis and contralateral hemiataxia. Patient 3 without hemiataxia showed infarction of the red nucleus but not the decussation. Only with large lesions and combined oculomotor deficits, in some exceeding the usual thalamopeduncular territory, did we observe severe contralateral weakness consistent with Weber's syndrome [42]. With more extensive involvement of the red nucleus (Patients 10 and 11), there was delayed tremor.

Neurobehavioral Syndromes

Altered consciousness, including states such as hypersomnia [43, 44], akinetic mutism [3, 45], or even deep unremitting coma [9], is a feature of bilateral paramedian thalamic infarction [35, 46, 47]. All four patients in Group 2 presented with stupor or coma at onset. Overall, impaired consciousness was associated with the presence of bilateral damage, some with typical "butterfly-shaped" lesions [3]. Interruption of the ascending noradrenergic pathways traveling in the paramedian tegmental region [46] or damage to the intralaminar nuclei [35, 48], the rostral extension of the MRF, have been held responsible for depressed alertness.

An amnesic state, in some patients severe enough to warrant the term "thalamic dementia" [35, 49–51], is another recognized effect of bilateral or unilateral lesions affecting the thalamopeduncular junction and paramedian thalamic nuclei. The specific anatomical site for dysmemory from diencephalic damage is unsettled, although the median or dorsomedial nucleus [35, 47, 51–55], the ventral anterior formation [19, 49, 56], and the mamillothalamic tract [48, 50, 57, 58] have each been implicated. Patient 7 had the most severe amnesic syndrome with only a small thalamic component that did not include the median nucleus. However, there was an infarct ventral and medial to

the left red nucleus, in the region of the mamillothalamic tract. Other patients in our series with dorsomedial thalamic involvement alone had mild and transient disturbances of memory, as others have noted clinically [9, 59] and experimentally [60, 61]. Our findings support claims implicating the mamillothalamic tract or ventral anterior nuclear tier, rather than the median nucleus, in causing severe amnesic states [62, 63].

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