

The human basis pontis: motor syndromes and topographic organization

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Summary

Clinical-anatomic correlations were performed in 25 patients with focal infarcts in the basilar pons to determine whether pontine lacunar syndromes conform to discrete clinical entities, and whether there is topographic organization of the motor system within the human basis pontis. Twelve clinical signs were scored on a 6-point scale, neuroimaging lesions were mapped and defined with statistical certainty, and structure-function correlation was performed to develop a topographic map of motor function. Clinical findings ranged from major devastation following extensive lesions (pure motor hemiplegia) to incomplete basilar pontine syndrome and restricted deficits after small focal lesions (ataxic hemiparesis, dysarthria–clumsy hand syndrome, dysarthria–dysmetria and dysarthria–facial paresis). The syndromes are not absolutely discrete, and are distinguished from each other by the relative degree of involvement of each clinical feature. Structure–function correlations indicate that strength is conveyed by the corticofugal fibres destined for the spinal cord, whereas dysmetria results from lesions involving the neurons of the basilar pons that link the ipsilateral cerebral cortex with the contralateral cerebellar hemisphere. Facial

movement and articulation are localized to rostral and medial basilar pons; hand coordination is medial and ventral in rostral and mid-pons; and arm function is represented ventral and lateral to the hand. Leg coordination is in the caudal half of the pons, with lateral predominance. Swallowing is dependent upon the integrity of a number of regions in the rostral pons. Gait is in medial and lateral locations throughout the rostral–caudal extent of the pons. Dysmetria ipsilateral to the lesion constitutes a disconnection syndrome, as it occurs when the hemipontine lesion is extensive and interrupts pontocerebellar fibres traversing from the opposite, intact side of the pons. The heterogeneity of manifestations reflects the well-organized topography of motor function in the human basis pontis, in agreement with the anatomic organization of the motor corticopontine projections in the monkey. Higher order impairments including motor neglect, paraphasic errors and pathological laughter result from rostral and medial pontine lesions, and may result from disruption of the pontine component of associative corticopontocerebellar circuits.

Keywords: pons; lacune; dysmetria; dysarthria; topography

Abbreviations: AH = atactic hemiparesis; DCH = dysarthria–clumsy hand; DD = dysarthria–dysmetria; DF = dysarthria–facial paresis; DWI = diffusion-weighted imaging; IBPS = incomplete basilar pontine syndrome; NRTP = nucleus reticularis segmenti pontis; PMH = pure motor hemiplegia

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Introduction

The human basilar pons was described in 1573 by Costanzo Varolio (1543–1575), and the first reports of clinical manifestations of basilar pontine infarction began to appear three centuries later (Hayem, 1868; Hallopeau, 1876; Leyden, 1882; Joffroy and Letienne, 1891; Cohn, 1901; Marburg, 1911; Lhermitte and Trelles, 1934). These accounts were

complemented by detailed analyses of brainstem vascular anatomy (Duret, 1873; Stopford, 1916; Foix and Hillemand, 1926; Biemond, 1951) and clinical pathology (Kubik and Adams, 1946; Hiller, 1952; Denny Brown, 1953; Millikan and Siekert, 1955). Pontine infarction accounts for ~7% of stroke (Silverstein, 1964), and 15% of vertebrobasilar

Table 1 Patient identifying data and clinical findings

Case number	Age	Gender	R/L body	Face	Dysarthria	Dysphagia	Gait	Hand	Arm		Leg		Sensory	DTRs	Cognitive mood		
									Strength		Dexterity		Strength				
									Proximal	Distal	Strength	Strength	Proximal	Distal			
01	78	M	R	4	2	3	N/A	0	0	0	N/A	3	0	N/A	R gaze preference	N	
02	52	M	R	1	1	1	N/A	0	0	0	N/A	0	0	N/A	Slowed saccades	N	
03	60	M	R	3	2	2	2	3	2	4	3	4+	4	2	N	↑	
04	82	F	R	3	2	2	1	3	1	2	3	4	2	3	Left INO	N	
05	36	F	R	3	2	2	N/A	2	2	3	3	4	3	4	↓ pin and temp	↑	
06	59	M	L	3	3	5	4	3	1	4	4-	1	4+	3	↓ light touch	N	
07	71	M	R	3	2	3	3	4	2	5	4	2	4	3	On hand	↑	
08	49	F	L	3	2	5	4	4	3	4	4	4	4	3	R gaze	N	
09	77	M	R	3	2	5	2	4+	4+	4+	3	4+	4+	2	nystagmus	↑	
10	82	F	R	4	5	5	2	4	3	4-	4	4	4	4	↓ touch, pin, temp	↔	
11	58	F	L	3	4	5	2	2	0	3	4	1	4	2	F/A/L	N	
12	80	F	L	5	5	5	4	5	3	5	5	3	4+	5	Parasthesias at onset	Nocturnal confusion	
13	74	M	R	4	4	3	4+	4	4+	4+	3	4	4	2	N	↑	
14	50	M	L	4	4	5	3	4	2	5	4	1	4	2	N	↑	
15	41	F	L	4	4	5	4	4	3	4	4	2	4+	3	Paraesthesia at onset: N	Motor neglect	
16	32	M	R	4	4	5	5	5	3	4+	5	3	5	5	Hypo/hyper, N	↑	
17	75	F	L	4	4	5	4	4+	4+	4+	3	4	4	2	Sacc pursuit	N	
18	76	F	L	3	3	5	3	4+	4	4+	4	3	4+	4	Sacc pursuit	↑	
19	39	M	L	3	4	4	4	4	2	4	4	4	4	4	Left arm numb., to R but N testing	Motor neglect	
20	64	M	L	3	3	4	1	1	1	2	2	2	4	5	Decreased pin, F/A	↑	
21	55	M	R	3	3	4	3	5	2	5	4+	2	5	5	Sacc pursuit	↓ word finding, fluency to R	

Table 1 *Continued*

Case number	Age	Gender	R/L body	Face	Dysarthria	Dysphagia	Gait	Hand	Arm		Leg		Eyes		Sensory	DTRs	Cognitive mood		
									Strength		Dexterity		Strength		Dysmetria				
									Proximal	Distal	Proximal	Distal	Proximal	Distal	Proximal	Distal			
22	61	M	L	4	2	5	3	5	2	5	5	2	5	2	N	Parasthesia	↓	N	
23	62	M	L	5	2	5	N/A	4	3	4	4	3	4	4	R VI	arm, leg: N	N/A	N	
24R	55	M	R	0	1	0	N/A	4	3	4	4	3	4	4	3	Nystagmus sacc pursuit	↑ (AKA)	Depression	
24L	62	F	L	1	1	0	N/A	5	4	5	4	4+	4	5	4	Nystagmus N	↑ at onset	Depression Confusion	
25			R	2	2	1	4	4+	4	4+	4	4	5	5	5	N			

Motor: MRC grading, 0 absent; 1 flicker of movement; 2 movement in plane of gravity; 3 movement against gravity; 4 decreased against resistance (4–, 4, 4+); 5 full power. Facial weakness, hand dexterity, extremity dysmetria, dysarthria and dysphagia: 6-point grading system. 0 no residual discernible; 1 severely abnormal, residual function minimal or barely perceptible; 2 moderately abnormally, function degraded sufficiently that useful performance is prevented; 3 mildly abnormal, deficit clearly present, function impaired but possible; 4 minimally abnormal, impairment just detectable; 5 normal. Gait: 0 gait impossible; 1 severely impaired, possible only with personal assistant; 2 moderately impaired, possible only with walker; 3 mildly unstable, walks independently necessitating use of a cane; 4 minimally unsteady and walks independently; 5 normal. AKA = above knee amputation; DTRs = deep tendon reflexes; F/A/L = face, arm and leg; hyper = hypermetric; hypo = hypometric; INO = internuclear ophthalmoplegia; L = left; N = normal; N/A = not applicable; R = right; sacc = saccadic; temp = temperature; VI, VII cranial nerve.

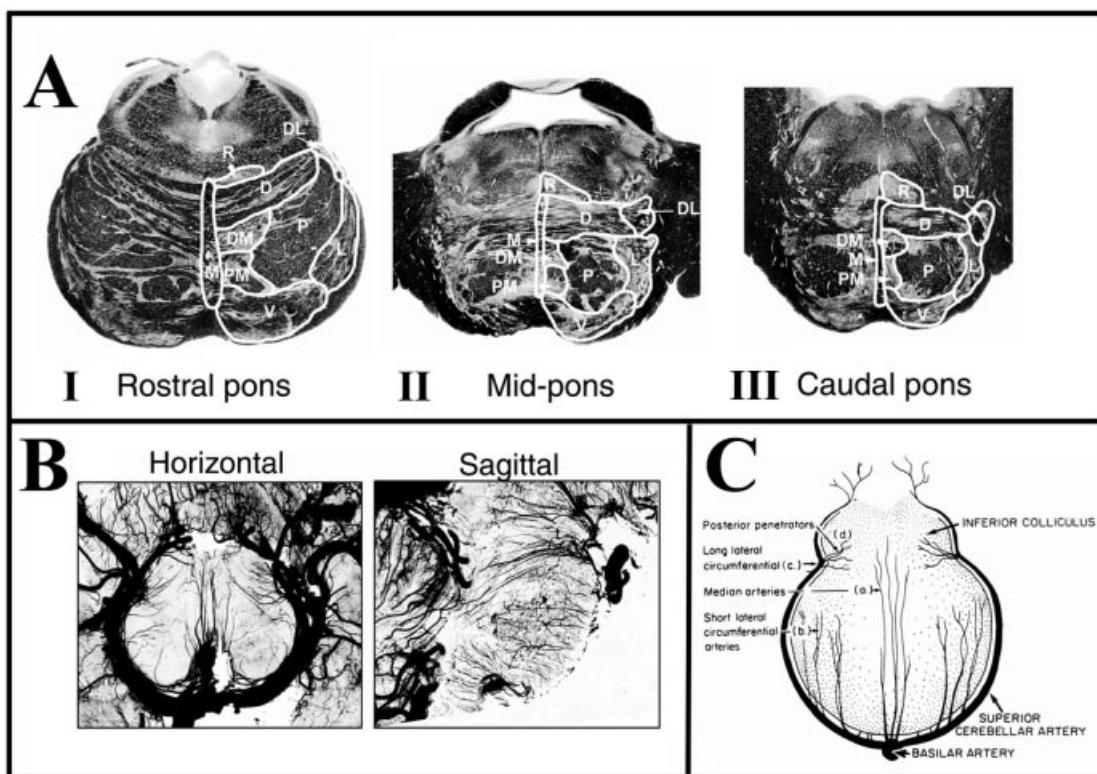


Fig. 1 (A) Basilar pontine nuclei in human. Three rostral to caudal levels (I, II and III) of pons in the transverse plane show corticofugal fibres that descend through the peduncle to the medulla; pontine neurons interspersed by, situated within and circumferentially around the corticofugal fibres; and pontocerebellar fibres that travel horizontally through the opposite hemipons to the contralateral cerebellum. D = dorsal pontine nucleus; DM = dorsomedial; DL = dorsolateral; L = lateral; M = median; P = peduncular (intrapeduncular versus peripeduncular not specifically identified); PM = paramedian; V = ventral; R = nucleus reticularis segmenti pontis. Myelin-stained pons template from DeArmond *et al.* (1976). Nuclear subdivisions and nomenclature derived from monkey, in Nyby and Jansen (1951) and Schmahmann and Pandya (1989). (B) Vascular supply of pons. The myriad arterioles accounting for variations of anatomy of ischaemic lesions, shown in the dye injections of Salamon (1971). (C) Schematic of pontine vascular anatomy, showing median (a), and anteromedial and anterolateral branches (b) of the short circumferential arteries, according to Amarenco *et al.* (1998).

ischaemic disease (Bassetti *et al.*, 1996). In the autopsy study of Silverstein (1964), all but two of 74 cases of pontine infarction were unilaterally situated in the upper third and mid-pons. Hemiparesis occurred when the stroke lay in the path of the corticospinal tracts, and cerebellar syndromes resulted from lateral pontine lesions. The concept of lacunar infarction was introduced by Marie (1901), and C. Miller Fisher described the pontine lacunar syndromes of pure motor hemiplegia (PMH) (Fisher and Curry, 1965), atactic hemiparesis (AH) (Fisher and Cole, 1965; Fisher, 1967) and dysarthria–clumsy hand (DCH) syndrome (Fisher, 1967).

These pontine syndromes subsequently have been verified (e.g. Glass *et al.*, 1990; Kim *et al.*, 1995; Moulin *et al.*, 1995; Bassetti *et al.*, 1996; Gorman *et al.*, 1998), and new entities have been added including dysarthria–facial paresis (DF) (Hopf *et al.*, 1990; Kim, 1994), pure dysarthria and isolated facial paresis (Kim, 1994).

It remains unclear whether the pontine lacunar syndromes are distinctly different, or whether they are variations of the same entity. How ‘pure’ must each syndrome be to warrant

the correct designation, and can they indeed be ‘pure’? Fisher considered the different presentations to be a manifestation of the anatomical arrangement of the corticofugal system in the basilar pons, but the precise relationship of the lesions to anatomy within the pons has not been established.

In the monkey, the basis pontis receives topographically arranged projections from sensorimotor (Nyby and Jansen, 1951; Brodal, 1978; Hartmann-von Monakow, 1981; Schmahmann and Pandya, 1995a; Schmahmann *et al.*, 2004a) as well as associative and paralimbic cortices (Schmahmann and Pandya, 1997a, b). Motor corticopontine projections from the face region of the supplementary motor area (SMA) form a complex mosaic medially and ventrally at all rostral to caudal levels of the pons; those from primary motor cortex (M1) face area terminate lateral to the SMA face area; arm terminations are situated within a semicircular region at the medial part of the pons; and leg terminations form an interrupted ring around the caudal half of the pontine nuclei with a lateral predominance. The pontine territories of these different motor areas are separate and overlap only minimally (Schmahmann *et al.*, 2004a, b). It is not known

whether there is a similar degree of topographic organization in the motor corticopontine pathways in the human.

In this study, therefore, we set out to determine two separate but related goals. First, whether a finer understanding of the anatomy and clinical manifestations of focal infarction in the basilar pons might help to elucidate further the pontine lacunar syndromes, and secondly, whether there is topographic organization of motor (and possibly also non-motor) systems in the human basis pontis. As tract tracer studies in the human are not feasible, we reasoned that it might be possible to address these questions by detailed analysis of the clinical consequences of focal ischaemic lesions of the pons.

Methods

Patient selection

Patients with acute focal infarction confined to the basilar pons were examined (J.D.S.) prospectively over 8 years at the Massachusetts General Hospital during the routine course of clinical practice. Complete neurological examinations were performed in all patients. One came to attention through the neuropathology brain-cutting exercise, and the notes of the neurology team were reviewed. All but one (with an implanted metal device) were evaluated using MRI. Exclusion criteria were pre-existent brain disease or acute lesions elsewhere in the brainstem, cerebellum or cerebral hemispheres. Unrelated neurological features present in one patient each included remote history of frontal contusion, white matter disease on MRI, and peroneal neuropathy. Four patients had diabetic neuropathy. The use of previously acquired neurological, radiological and pathological information for the purposes of this study was approved by the Human Studies Committee of the Massachusetts General Hospital.

Quantitation of clinical results

Clinical features were evaluated quantitatively to facilitate lesion-deficit correlations. Motor deficits were characterized with the Medical Research Council (1976) 6-point grading system. Grade 4 weakness was subdivided into 4-, 4 and 4+ to categorize patients into syndromes, but for statistical analysis grade 4 was considered as a whole. Six-point grading systems were used to determine severity of dysmetria, facial paresis, dysarthria, dysphagia and gait (see Table 1). Most patients were examined more than once during their hospital stay. The pattern and severity of deficits were documented only after the neurological presentation stabilized, usually within 2–3 days of onset. Herald symptoms including slurring of speech or instability of gait that lasted only a matter of hours were not graded as fixed deficits.

Determination of ataxia/dysmetria

Ataxia/dysmetria as a sign of cerebellar system involvement apart from weakness was determined as described by Holmes (1939) and the International Cooperative Ataxia Rating Scale (Trouillas *et al.*, 1997). Upper extremity dysmetria was characterized by side-to-side or vertical oscillation at end points with finger-to-nose test, overshoot with rapid finger following, irregular rate, rhythm and force of rapid hand and finger tapping, dysdiadochokinesis and exaggerated arm rebound. Lower extremity dysmetria was deter-

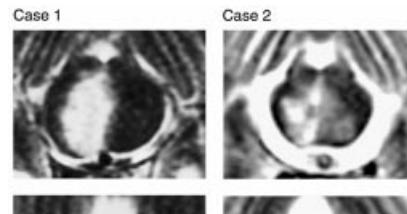


Fig. 2 T2-weighted MRI scans of patients with the complete basilar pontine syndrome, or pure motor hemiplegia. In these and subsequent images, the right hemipons is on the right side of the figure.

mined by proximal overshoot and lateral movements with heel-to-shin test, decomposition of movement and irregularity in rate, rhythm and force of foot tapping. Ataxic gait veered to the side or misplaced the leg laterally.

Lesion identification with neuroimaging

Pontine infarction was identified on routine clinical MRI (CT in case 3). The MRI scans were performed on a GE 1.5 T scanner, at 5 mm slice thickness, 1 mm spacing between slices, field of view (FOV) 220. For T1 images, TR was 450 ms, TE 20 ms, ET 0 ms; for T2 images, TR was 6010 ms, TE 110 ms, ET 12 ms; for diffusion-weighted imaging (DWI), TR 7500 ms, TE 73 ms, ET 0 ms. The CT scan was acquired on a GE Lightspeed scanner, 140 kVp and 170 mA, FOV 220, 5 mm thick slices.

Lesion localization on neuroimaging scans

Precise characterization of lesions was required for structure-function correlation. The pons was present on three rostral to caudal levels. Images were imported into Adobe Photoshop 5.5 at a resolution of 300 pixels per inch. Rectangular grids were positioned over each half of the basilar pons and were individually sized to fit each of the three pontine levels in all 25 cases by linear scaling using the Free Transform Tool. The grid was divided into three medial to lateral zones, and four anterior-posterior zones, for a total of 12 sectors. Each sector was subdivided into 20 voxels, four across and five down, for a total of 240 voxels per hemipontine level. Voxels in this rectangular grid located outside the pons were excluded from analysis.

Basilar pontine nuclear topography

The nuclei within the basilar pons of the rhesus monkey (Nyby and Jansen, 1951; Schmahmann and Pandya, 1989) were used to derive outlines of pontine regions within the human basis pontis. The pontine nuclei are to some degree architectonically distinct in the

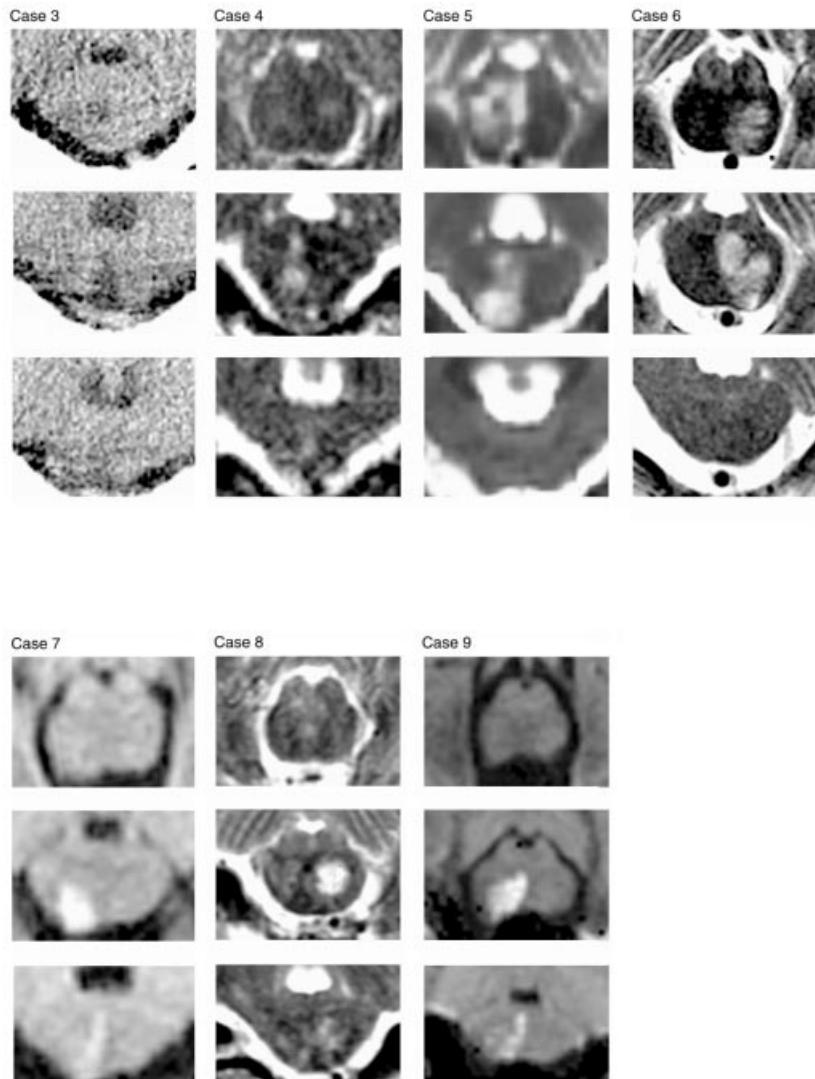


Fig. 3 Neuroimaging scans of patients with incomplete basilar pontine syndrome. CT scan in case 3, T2-weighted MRI in cases 4, 5, 6 and 8; and DWI in cases 7 and 9.

monkey, but this has not been shown in human. The human pontine subdivisions are thus based solely on geographic location (Fig. 1).

Data analysis

Clinical signs

Twelve clinical signs were quantitatively analysed: dysarthria, dysphagia, facial paresis, hand dexterity, hand strength, arm dysmetria, proximal arm strength, distal arm strength, leg dysmetria, proximal leg strength, distal leg strength and gait. The clinical presentations were categorized into six syndromes, and the validity of this grouping was tested by analysis of variance (ANOVA) that examined the effect of group membership on the clinical symptoms. *Post hoc* comparisons among groups were made with the Tukey's HSD (honestly) test. Factor analysis of the clinical symptoms was performed using principal component analysis (PCA) with Varimax rotation. The number of meaningful factors for rotation was determined on the basis of two criteria: (i) eigenvalues of factors to be retained greater than 1; and (ii) visual examination of the scree

plot. Factor score was calculated by the regression method and used to characterize group differences graphically. Statistical analyses were performed using SPSS version 10.0.

Neuroimaging lesion analysis

The boundary between normal and infarcted tissue was determined as follows.

Voxel intensity

Using the Magnification Tool and the Magic Wand cursor, the image intensity of the central pixel in each voxel was determined, ranging from 0 to 100% on grey scale. The single pixel intensity was taken to represent the intensity of that voxel. This approach was validated in 10 voxels (one per decile), as measured intensity of the central pixel was no different from the mean of the measurements of all pixels in that voxel ($P = 0.999$).

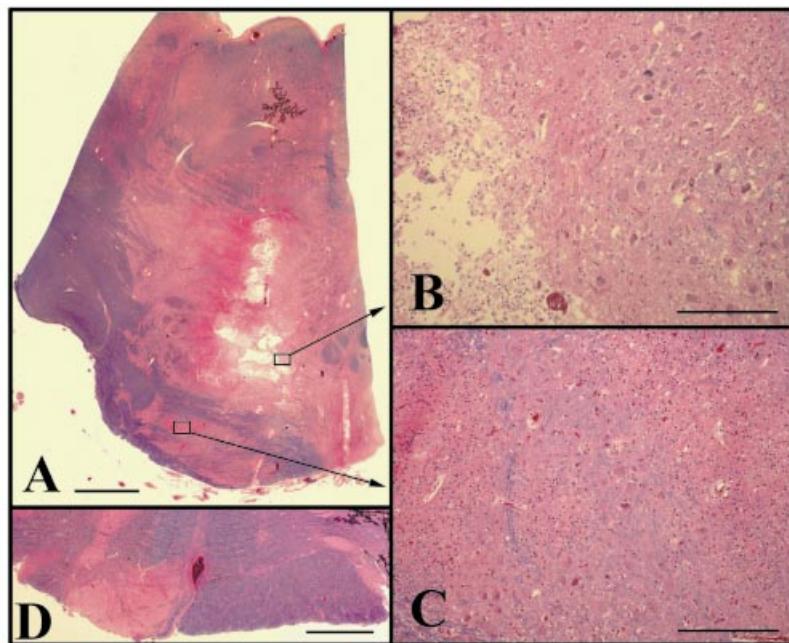


Fig. 4 Pathology in case 4 (compare with MRI in Fig. 3). Pontine infarction in level II (A), with demarcated areas showing necrosis of pyramidal and pontocerebellar fibres and loss of basilar pontine neurons in (B), and mild gliosis but intact pontine neurons in (C). Wallerian degeneration in the pyramidal tract in the medulla resulting from the pontine lesion is in (D). (A, bar = 5.0 mm; B and C, bar = 0.2 mm; D, bar = 1.0 mm. Haematoxylin and eosin. Pathology slides courtesy of Massachusetts General Hospital Department of Neuropathology).

Defining infarcted voxels

Normal voxels in pontine regions ipsilateral and contralateral to the lesion were defined by visual inspection, to determine the range of normal intensities. The range of non-normal tissue was defined as voxels with intensity scores below that of normal tissue. (For one MRI and the CT, images were inverted to maintain the direction of this relationship.) The distribution of non-normal voxel scores was used to define a cut-off score using a criterion of $P = 0.05$ (one-tailed). Infarcted voxels were then defined as non-normal voxels with an intensity score at or below the cut-off.

Normalization

The unit measurement of intensity (the gradient percentage scale score) differed between cases because the ranges of signal intensities of the scans were different. A normalization procedure was therefore performed to achieve a constant interval between scores. The gradient percentage score of every voxel (X) in each patient was transformed to a score with constant measurement (Y) using the following function, in which voxels equal to S (infarcted) are scaled to an arbitrary value A, and those voxels equal to N (normal) to an arbitrary value B.

$$Y = (X - S)/(N - S) \times A + (X - N)/(S - N) \times B$$

Clinical-anatomical correlation

The relationship between pontine regions and clinical manifestations was evaluated to determine a topographic map of motor representation in the pons. Spearman rank correlation analysis was performed between the clinical symptoms, each of which was

graded on a 6-point scale, and the intensity score of each voxel (along a continuous gradient within a defined range of infarcted tissue). All cases were analysed without regard to laterality, and depicted arbitrarily on the right side.

Methodological considerations

In order to be certain that the neuroimaging lesion truly reflected brain pathology, the boundary of the neuroimaging lesion was defined with statistical certainty. The validity of this method was confirmed by comparison of the pathological findings with the neuroimaging features in two cases: T2-weighted image in case 4 (Figs 3 and 4) and DWI in case 23 (Figs 7 and 8). The extent of the lesion was consistent with that determined from the MRI in both cases. The superimposition of our voxel map on the pons template of DeArmond *et al.* (1976) leaves one to two voxels at the ventral midline apparently outside the pons; this is an artefact reflecting the difference between the template and the actual MRI scans.

Results

Twenty-five patients (15 men, 10 women; age range 28–82, mean 62.0 years, SD 15.6) were studied. Extremity and facial deficits were right sided in 12, left sided in 12, and bilateral in one (Table 1). By comparing the severity of the different motor features, the presentations could be grouped into six clinical syndromes. These are summarized below, and synopses of case histories of patients in each category are given in Table 2.

Table 2 Synopsis of case histories

Pure motor hemiplegia

Case 1

A 78-year-old man with hyperlipidaemia, with acute right-sided weakness progressing over hours. He had hypophonia, moderate dysarthria, dysphagia and facial paresis, right gaze preference, and right hemiplegia except hip strength 4–, hyper-reflexia, extensor plantar response and normal sensation. Left side had full power, with dysmetria of the arm and leg. Ten days later, he was awake and attentive, with stuttering, paraphasic errors, agrammatism, impaired comprehension, naming impaired by semantic substitution, repetition impaired for non-words, and perseveration with verbal and motor responses. Declarative learning was intact, but he required multiple choice for recall.

Case 2

A 52-year-old man with hypertension and hyperlipidaemia developed a distal basilar artery embolus with headache and slurred speech, followed the next day by right-sided paralysis. He was obtunded. Two weeks later, he had severe dysarthria and dysphagia, slowed saccades, right facial paresis, flaccid right-sided paralysis, hyper-reflexia and extensor plantar response, and normal sensation. Strength was full on the left, with prominent dysmetria of the arm and leg.

Incomplete basilar pontine syndrome

Case 3

A 60-year-old man with diabetes and hypertension awoke with wobbly gait, slurred speech, and right arm problems that worsened over 2 h. The next day, he had moderate right facial paresis and dysarthria, arm drift, decreased upper extremity power more notable distally, mild leg weakness, hyper-reflexia with extensor plantar response, and diabetic neuropathy. He had severely impaired fine finger movements, inability to do buttons, and arm and leg dysmetria.

Case 4

An 82-year-old woman with hypertension awoke with dysarthria, right leg weakness and gait impairment. Mild hemiparesis and dysarthria progressed to flaccid hemiplegia and severe dysarthria, facial paresis and dysphagia. Proximal arm and leg strength recovered over 2 days to demonstrate marked dysmetria. She had right hyper-reflexia, extensor plantar response, severely impaired gait, and normal sensation and eye movement. Depression was prominent. Magnetic resonance angiography (MRA) showed vertebrobasilar atherosclerosis. She expired from intracranial haemorrhage 4 years later. Pontine pathology is shown in Fig. 4.

Case 5

A 36-year-old woman embolized to the basilar artery from a patent foramen ovale with right-to-left shunt. She developed acute vertigo, diplopia, severe dysarthria, left internuclear ophthalmoplegia, right face, arm and leg hemiparesis, hyper-reflexia, extensor plantar response, and arm and leg dysmetria with decreased pin and temperature appreciation. She ambulated independently at 2 months, with residual AH.

Case 6

A 59-year-old man with 2 days of impaired balance, slurred speech, left arm weakness and clumsiness. He had dysarthria, left face, arm and leg hemiparesis, hyper-reflexia, extensor plantar, prominent dysmetria of arm and leg, poor hand dexterity and decreased touch on the arm. Melena during hospitalization led to diagnosis of colon carcinoma.

Case 7

A 71-year-old man with diabetes, hypertension, peripheral vascular disease and coronary artery disease. He had acute right arm more than leg weakness, incoordination and difficulty rising from a chair. Examination the next day revealed prominent dysarthria, dysphagia, nystagmus with right lateral gaze, right face, arm and leg hemiparesis, hyper-reflexia, extensor plantar response, upper and lower extremity dysmetria, poor hand dexterity and wide-based unsteady gait. Sensation was normal except for diabetic neuropathy.

Case 8

A 49-year-old woman had acute onset of progressive left arm tingling, weakness and slurred speech. Examination 2 days later revealed dysarthria, mild left face, arm and leg hemiparesis, arm and leg dysmetria, impaired hand dexterity, mute plantar response, and decreased touch, pin and temperature on the left face. MRA revealed carotid siphon atherosclerosis.

Case 9

A 77-year-old man with hyperlipidaemia and hypertension and stuttering course over 12 h of the right leg then arm prickling, gait unsteadiness, leaning to the right, dysarthria, nausea and vomiting. He had mild right facial, dysarthria, and arm and leg weakness, but moderately severe dysmetria in the leg more than the arm and hand. Gait was ataxic and required a walker. He had right hyper-reflexia but normal plantar response and sensation.

Ataxic hemiparesis

Case 10

An 82-year-old woman awoke with acute loss of right eye vision (central retinal artery occlusion), and decreased hand dexterity, strength and coordination of the arm and leg on the right. She had normal speech and swallowing; facial movements were symmetric but the right activated slowly. She also had mild proximal right arm and leg weakness, leg dysmetria more than the arm, hyper-reflexia, extensor plantar response and normal sensation. No embolic source was found.

Table 2 *Continued***Case 11**

A 58-year-old woman with hypertension and coronary artery disease developed mild dysarthria, facial asymmetry and left leg incoordination. On day 2 she had subtle left facial asymmetry and dysarthria, motor neglect, arm strength moderately impaired proximally and severely decreased in the fingers (too weak for dysmetria evaluation), her leg was weak distally with dysmetria, hyper-reflexia, extensor plantar response and normal sensation. On day 3 there was no dysarthria or facial asymmetry; but she had distal predominant arm and leg weakness, arm overshoot with rapid finger following, side-to-side dysmetria and poor hand dexterity. Gait required two assistants. There was subtle dysmetria of the right arm and leg.

Case 12

An 80-year-old woman with hypertension and hyperlipidaemia. She awoke with nausea, vomiting, imbalance and tingling in the left hand and foot. Her face was symmetric, and she had no dysarthria. Strength was normal in the left arm, decreased proximally in the leg, with arm and leg dysmetria, extensor plantar response, and hyperaesthesia in the left hand. She walked alone but stumbled to the left. MRA revealed severe right vertebral artery stenosis.

Case 13

A 74-year-old man with diabetes, hypertension, coronary artery disease and hyperlipidaemia developed impaired gait and slurred speech while working in the yard. There was subtle right facial flattening, lingual dysarthria, mild weakness of the right arm and leg with arm and leg dysmetria, unsteady gait veering to the right, hyper-reflexia, extensor plantar response and normal sensation except for diabetic neuropathy.

Case 14

A 50-year-old man with diabetes and hypertension awoke with imbalance and slurred speech. He had saccadic pursuit, subtle facial asymmetry and dysarthria. Strength was moderately impaired in the left arm and leg, worse distally, with prominent arm and leg dysmetria and poor hand dexterity. He had slow, hemiparetic and unsteady gait, left hyper-reflexia, mute plantar response and normal sensation. There was minimal overshoot with rapid finger following with the right arm.

Case 15

A 41-year-old woman with atherosclerosis and cocaine use developed acute nausea and incoordination, followed the next morning by left-sided tingling and arm heaviness, and thick speech. Examination a day later showed normal speech and eye movements, minimal weakness of the left arm and leg, but prominent dysmetria of the arm and leg, slow and unsteady gait, hyper-reflexia, extensor plantar response and normal sensation.

Case 16

A 32-year-old man developed acute difficulty controlling the left arm, unstable gait and tongue 'thickness'. He had minimal dysarthria, subtle facial asymmetry, mild weakness of the left arm, preserved hand strength but poor hand dexterity, and dysmetria of the arm. The leg, gait, reflexes and sensation were normal. No embolic source was identified.

Case 17

A 75-year-old woman with acute vomiting, vertigo, dysarthria and difficulty using the left arm. She had minimal facial asymmetry and lingual dysarthria, saccadic intrusions into pursuit, mild weakness of the left leg more than the arm. Dysmetria was pronounced, the leg more than the arm, and finger movements were slowed. She had unsteady gait, lower extremity hyper-reflexia, flexor plantar responses and normal sensation. Dolichoectatic vertebrobasilar system on MRA.

Case 18

A 76-year-old woman with diabetes and hypertension awoke with vertigo, difficulty lifting the left leg, left arm heaviness, slurred speech and left facial flattening. The following day there was minimal dysarthria and facial asymmetry, mild decreased strength in the left arm more pronounced distally, slight leg weakness, dysmetria of the arm and leg, independent but unsteady gait with widened base, and normal reflexes and sensation.

Dysarthria—clumsy hand**Case 19**

A 39-year-old man with intravenous drug abuse developed acute nausea, left-sided weakness and numbness. He had saccadic intrusion into pursuit to the right, left facial flattening and dysarthria. There was motor neglect of the left side despite only trace weakness, dysmetria of the arm more than the leg, prominently impaired finger dexterity, mildly unsteady gait, left hyper-reflexia and extensor plantar response with normal sensation.

Case 20

A 64-year-old man with diabetes and coronary artery disease awoke unable to walk. Later he noted slurred speech and left-sided weakness. There was moderate dysarthria and left facial asymmetry, minimal movement of the left hand and severely compromised dexterity, and moderately decreased arm strength with dysmetria. Left leg strength was mildly decreased, with hyper-reflexia and extensor plantar response. He had decreased pin sensation in the left face and arm.

Table 2 *Continued***Case 21**

A 55-year-old man with diabetes and hypertension awoke with dizziness, imbalance and lingual dysarthria with disordered rate, rhythm and volume; saccadic pursuit, hypometric saccades; subtle right facial flattening; minimal weakness of the right arm and hand; mild arm dysmetria; and markedly poor hand dexterity. His leg was near normal with unsteady gait. He had right hyper-reflexia and extensor plantar response, and peripheral neuropathy. He had word-finding difficulty, and reduced verbal fluency (phonemic, 4 A words, 7 F words; semantic, 14 animals). There were no paraphasic errors, and repetition was normal.

Dysarthria–dysmetria**Case 22**

A 61-year-old man with diabetes and hypertension noted 3 days of gait instability, slurred speech, left hand clumsiness and transient numbness of the left arm and leg. Examination revealed lingual and palatal predominant dysarthria, normal strength, unstable gait and poor coordination of the left arm and leg. Reflexes were symmetric, plantar responses flexor, and he had peripheral polyneuropathy.

Case 23

A 62-year-old man with diffuse vascular disease, systemic lupus erythematosus, atrial fibrillation and left above knee amputation acutely developed dysarthria. Examination revealed right VIth nerve palsy, moderate dysarthria, minimal weakness of the left arm and hip, but prominent dysmetria, dysdiadochokinesis and impaired hand dexterity. He succumbed 5 months later to bronchopneumonia. The pathology of the pons is shown in Fig. 8.

Dysarthria–facial paresis**Case 24**

A 55-year-old man with acute vertigo, vomiting diplopia and imbalance from an embolus to the distal basilar artery. Dysarthria and right-sided incoordination worsened. He had nystagmus in all positions of gaze, maximal to right, near-complete facial diplegia, severe dysphagia and profound dysarthria. Strength was minimally decreased on the right with a trace of dysmetria, reflexes were normal, bilateral Babinski signs, sensation was preserved. Depression required treatment.

Case 25

A 62-year-old woman with diabetes and hypertension awoke with slurred speech, facial asymmetry and impaired gait. She had right facial paresis, lingual predominant dysarthria and prominent dysphagia. Strength was normal with no dysmetria. Reflexes, plantar responses and sensation were normal.

Pontine syndromes

Complete basilar pontine syndrome–pure motor hemiplegia (PMH)

Clinical. In patients 1 and 2, there was complete or near-complete paralysis of contralateral arm and leg, with severe facial paresis, dysarthria and dysphagia. Paralysis of gaze to the side ipsilateral to the lesion was consistent with involvement of the tegmentum. Aphasia with agrammatism, and confusion, were present in case 1, and decreased arousal in case 2. Contralateral hyper-reflexia and extensor plantar responses were noted in both cases, and there was prominent dysmetria of the arm and leg ipsilateral to the lesion.

Anatomy. The lesions were large (Fig. 2), and involved essentially all regions of the basilar pons, i.e. the intrapeduncular, peripeduncular, median, paramedian, dorsomedial, dorsal, dorsolateral, ventral, lateral and reticular pontine regions. The entire rostral-caudal extent of the pons was involved in case 1, and the rostral two-thirds in case 2.

Incomplete basilar pontine syndrome (IBPS)

Clinical. All the motor features evaluated were abnormal in seven patients (cases 3–9), with varying severity. This included dysmetria and weakness in the contralateral limbs, impaired dexterity and power in the hand, facial paresis, dysarthria and dysphagia. The severity of each deficit within this constellation varied according to the extent of the lesion. All had mild facial weakness and moderate dysarthria. Cases 3–6 had relatively greater upper extremity involvement; in cases 7–9, the leg was somewhat more involved. Hyper-reflexia and extensor plantar responses were evident in the affected extremities in all.

Anatomy. The lesions were similar to, but less extensive than PMH, and involved multiple pontine regions in two-thirds of the pons in the rostro-caudal dimension (Fig. 3). These included the intrapeduncular, peripeduncular, median, paramedian, dorsomedial, ventral, lateral and dorsal pontine regions. Cases with greater upper extremity involvement had lesions that mostly involved pontine level 2; when the leg was more involved, infarction was prominent also in pontine level

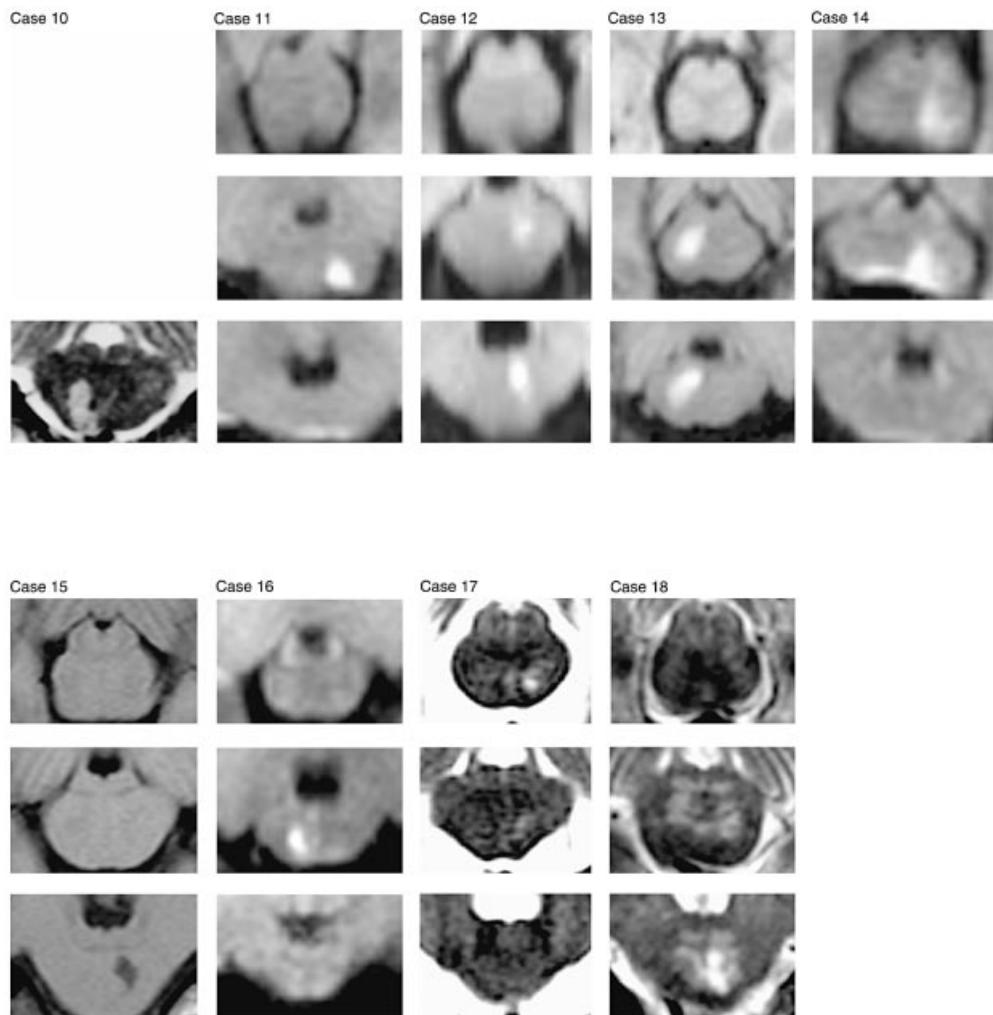


Fig. 5 MRI scans of patients with ataxic hemiparesis. T2-weighted MRI in cases 10, 17 and 18; DWI in cases 11, 12, 13, 14, 16; and T1-weighted MRI in case 15.

3. Internuclear ophthalmoplegia (case 5) and a mild decrease in sensation to pin, temperature and touch (cases 5, 6 and 8) reflected involvement of the medial tegmentum. The neuroimaging lesion in case 4 was confirmed pathologically (Fig. 4).

Ataxic hemiparesis (AH)

Clinical. Nine patients (cases 10–18) demonstrated weakness and dysmetria of the contralateral arm and leg. There was no, or barely perceptible, facial asymmetry or dysarthria, and no dysphagia. Gait was impaired to varying degrees, except in one patient (case 16) with sparing of the leg, in whom gait was essentially normal. Contralateral hyper-reflexia and extensor plantar responses were noted. All modalities of sensation were normal, although patient 15 experienced paraesthesia in the limbs at onset.

Anatomy. The lesions were discrete and focused in the middle and/or caudal thirds of the pons, in either one or two levels (Fig. 5). They were situated in or around the descending corticofugal fibres and involved the intrapeduncular, peri-peduncular, dorsal and ventral pontine regions.

Dysarthria–clumsy hand (DCH)

Clinical. Three patients (cases 19–21) demonstrated dysarthria and facial paresis accompanied by mild weakness of the intrinsic hand muscles, impaired finger dexterity, and mild weakness and dysmetria of the arm. In contrast, the leg was relatively spared. Hyper-reflexia and extensor plantar responses were evident. Case 19, with tegmental involvement, had subjective arm numbness. He also displayed motor neglect, such that he barely moved the limbs unless his attention was drawn to the affected extremity. Case 20, also

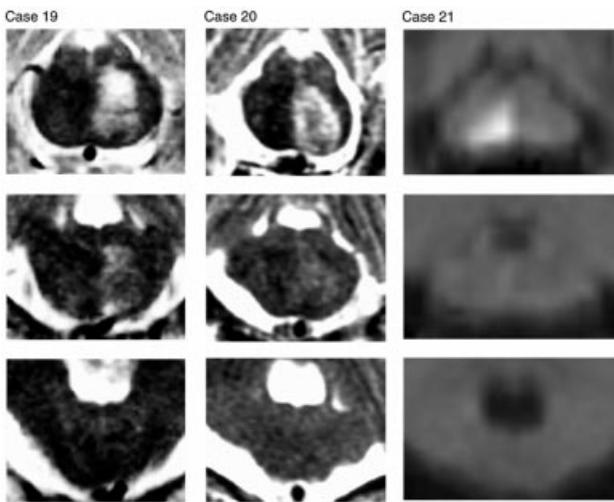


Fig. 6 Neuroimaging scans of patients with dysarthria–clumsy hand syndrome. T2-weighted MRI in cases 19 and 20; and DWI in case 21.

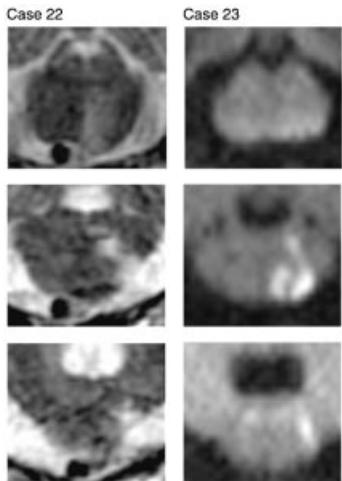


Fig. 7 Neuroimaging scans of patients with dysarthria–dysmetria. T2-weighted MRI in case 22; and DWI in case 23.

with tegmental involvement, had decreased pin sense in the face and arm. Case 21, who had no lesions outside the pons, complained of word-finding difficulty, and he had poor phonemic and semantic fluency.

Anatomy. The lesions were located in pontine level 1 (Fig. 6), and involved the median, dorsomedial and paramedian regions, and the medial and intermediate parts of the peripeduncular, intrapeduncular, ventral and dorsal regions.

Dysarthria–dysmetria (DD)

Clinical. In two patients, there was prominent dysarthria in the absence of dysphagia or facial weakness, along with dysmetria but no (case 22) or minimal (case 23) extremity weakness. Reflexes were symmetric and plantar responses

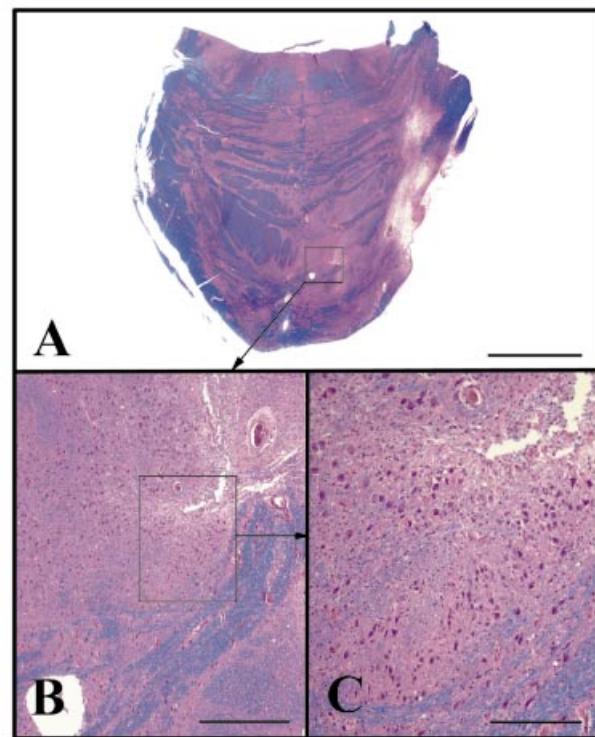


Fig. 8 Pathology in case 23 (compare with MRI in Fig. 7). Photomicrograph of the mid-caudal pons, equivalent to the rostral part of level III, in (A) showing the location of the infarct in the lateral pontine region. The image in B is taken from the demarcated area in A, and shows Wallerian degeneration of descending corticospinal pathways resulting from the infarct in the intrapeduncular region in the mid-pons, level II. The pontine neurons in the intrapeduncular region at this caudal level are intact, as shown in C. (A, bar = 10.0 mm; B, bar = 5.0 mm; C, bar = 0.2 mm. Haematoxylin and eosin. Slides courtesy of Massachusetts General Hospital Department of Neuropathology).

were flexor in case 21 (case 22 had undergone above knee amputation). Both had paraesthesia in the affected extremities at onset, but normal sensory examination.

Anatomy. The infarctions were situated in pontine levels 2 and 3 in the lateral and dorsolateral regions, and in the lateral parts of the ventral and dorsal regions (Fig. 7). Subtle facial flattening was noted in case 22 with a small lesion also in paramedian and medial parts of the peripeduncular region of pontine level 1. Slight arm and hip weakness occurred in case 23 who had an additional infarct in the intrapeduncular region. The neuroimaging lesion was confirmed pathologically in case 23 (Fig. 8).

Dysarthria–facial paresis (DF)

Clinical. In two patients, the constellation was notable for facial paresis, dysarthria and dysphagia. There was some dysmetria, but minimal or no extremity weakness. Plantar responses were extensor, and hyper-reflexia was variable.

Table 3 Analysis of variance of the 12 clinical signs quantitatively evaluated for the six clinical groups, and the post hoc analysis

	F	P	Post-hoc ^a
Face	9.054	0.000	2, 3, 4, 5 > 6
Dysarthria	21.837	0.000	3, 4 > 1, 2, 6; 3 > 5
Dysphagia	13.113	0.000	2, 3, 4, 5 > 6
Gait	2.387	NS	NA
Hand			
Strength	6.487	0.001	2, 3, 4, 5, 6 > 1
Dexterity	3.814	0.014	3, 6 > 1
Arm			
Proximal strength	8.872	0.000	2, 3, 4, 5, 6 > 1
Distal strength	19.198	0.000	2, 3, 4, 5, 6 > 1
Dysmetria	4.396	0.007	2, 3, 6 > 1
Leg			
Proximal strength	8.185	0.000	2, 3, 4, 5, 6 > 1
Distal strength	11.628	0.000	2, 3, 4, 5, 6 > 1
Dysmetria	6.576	0.001	2, 3, 4, 5, 6 > 1

^aTukey HSD, group 1 = PMH; group 2 = IBPS; group 3 = AH; group 4 = DCH; group 5 = DD; group 6 = DF; NS = not significant; NA = not applicable.

Case 24 had facial diplegia, profound hypophonic dysarthria, and dysphagia requiring tracheostomy and gastric feeding despite a good level of arousal, near normal strength with subtle dysmetria on the right, and mild ataxic hemiparesis on the left. DF in case 25 was associated with trace weakness and intention tremor of the left arm.

Anatomy. The consistent feature of these cases was involvement of the midline or adjacent parts of the basilar pons, namely the median, paramedian and dorsomedial regions, as well as the medial parts of the peripeduncular and ventral regions (Fig. 9). In case 24 with left weakness and dysmetria, the lesion also involved the right intrapeduncular region.

Validity of the clinical groups

ANOVA was used to examine the validity of these six clinical constellations (Table 3). Gait did not show significant group differences [$F(5,66) = 2.387, P > 0.05$]. The remaining 11 clinical signs showed significant differences among the six clinical groups: face [$F(5,66) = 9.504, P < 0.001$], dysarthria [$F(5,66) = 21.837, P < 0.001$], dysphagia [$F(5,66) = 13.113, P < 0.001$], hand strength [$F(5,66) = 6.487, P < 0.01$], hand dexterity [$F(5,66) = 3.814, P < 0.05$], arm proximal strength [$F(5,66) = 8.872, P < 0.001$], arm distal strength [$F(5,66) = 19.198, P < 0.001$], arm dysmetria [$F(5,66) = 4.396, P < 0.01$], leg proximal strength [$F(5,66) = 8.185, P < 0.001$], leg distal strength [$F(5,66) = 11.628, P < 0.001$] and leg dysmetria [$F(5,66) = 6.576, P < 0.01$].

Post hoc analysis was performed for clinical signs that showed significant group differences to determine which clinical groups were truly different (Table 3). Face score of

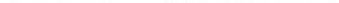
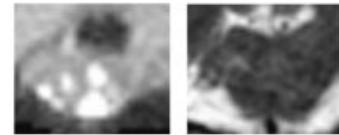
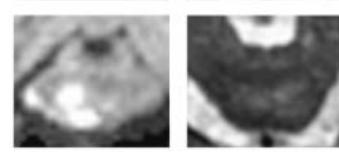
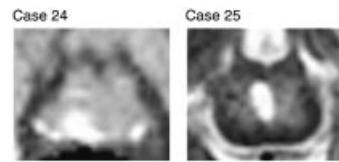


Fig. 9 Neuroimaging scans of patients with dysarthria–facial paresis. DWI in case 24; and T2-weighted MRI in case 25.

the DF group was worse than that of the IBPS ($P < 0.01$), AH ($P < 0.001$), DCH ($P < 0.05$) and DD ($P < 0.001$) groups. Compared with the AH group, dysarthria score was worse in the PMH ($P < 0.001$), IBPS ($P < 0.001$), DD ($P < 0.001$) and DF ($P < 0.01$) groups. Compared with the DCH group, dysarthria scores were worse in the PMH ($P < 0.05$), IBPS ($P < 0.05$), and DF ($P < 0.01$) groups. Dysphagia in the DF group was worse than in the IBPS ($P < 0.01$), AH ($P < 0.001$), DCH ($P < 0.01$) and DD ($P < 0.001$) groups. As expected, motor scores for the PMH group were significantly worse than other groups. Hand strength was worse in the PMH group compared with IBPS ($P < 0.01$), AH ($P < 0.01$), DCH ($P < 0.05$), DD ($P < 0.01$) and DF ($P < 0.01$) groups; proximal and distal strengths of the arm and leg were consistently worse than in the remaining five groups. Hand dexterity was worse in the PMH group compared with the AH and DF groups ($P < 0.05$).

Factor analysis

An alternative understanding of the grouping of the motor phenomena was derived from analysis of the extent to which the signs cluster together. From the 12 clinical signs, four factors that clustered the clinical symptoms together were extracted using PCA with Varimax rotation (Table 4). The KMO measure of sampling adequacy was superior level (0.811), and Bartlett test of sphericity confirmed that our data were appropriate for the factor analysis [$\chi^2(66) = 274.772, P < 0.001$]. The four factors accounted for 88% of the variance of the clinical syndromes (Fig. 10). Factor 1 (strength) accounted for ~34% of the common variance and included arm proximal and distal strength, hand strength, distal leg strength and gait. Factor 2 (cranial) accounted for ~24% of the common variance and included facial paresis, dysarthria and dysphagia. Factor 3 (upper extremity dysmetria) accounted for ~16% of the common variance and

Table 4 Principal component analysis of factor loading using the method of Varimax rotation for the 12 clinical signs in the 25 patients

	Factor				Community
	1	2	3	4	
Arm proximal strength	0.916	0.143	0.240	0.156	0.941
Arm distal strength	0.860	0.149	0.395	0.131	0.923
Hand strength	0.856	0.185	0.297	0.259	0.935
Leg distal strength	0.794	0.138	0.349	0.384	0.914
Gait	0.573	0.574	-2.2E-02	1.439E-03	0.667
Face	-1.3E-02	0.908	8.712E-02	-2.0E-02	0.833
Dysphagia	0.166	0.908	-5.3E-02	8.503E-03	0.855
Dysarthria	0.198	0.850	-2.2E-02	8.800E-02	0.762
Arm dysmetria	0.488	-9.9E-02	0.835	0.347	0.931
Hand dexterity	0.322	4.181E-02	0.833	9.615E-03	0.934
Leg dysmetria	0.233	-6.8E-02	0.132	0.930	0.942
Leg proximal strength	0.603	0.154	0.239	0.612	0.818
Eigenvalue	4.096	2.837	1.901	1.625	
% of variance	34.134	23.644	15.838	13.540	

The values in bold represent the clinical signs that cluster together as a group.

included hand dexterity and arm dysmetria. Factor 4 (lower extremity dysmetria) accounted for ~14% of the common variance and included leg dysmetria and proximal leg strength.

Lesion deficit correlation

The correlation of the pons lesion data with the scores of the 12 clinical signs produced a functional topographic map of the basilar pons (Figs 11–14).

Face

The lesioned voxels that correlated with facial weakness were located in medial pontine regions mostly in level I, but also in levels II and III (Figs 11A and 14). They occupied the median pontine nucleus predominantly, as well as the dorsomedial, paramedian and medial parts of the dorsal and ventral nuclei. Limited involvement was noted in the dorsolateral nucleus in level I.

Articulation

Dysarthria correlated mostly with levels I and II, with minor involvement of level III. Lesioned voxels were in the median, paramedian and dorsomedial nuclei, and the medial parts of the ventral and dorsal regions (Figs 11B and 14). Some voxels were identified in the medial part of the peripeduncular nucleus and in the lateral nucleus.

Swallowing

There were voxels widely spread throughout level I that correlated with dysphagia (Fig. 11B). With the exception of the intermediate aspects of the ventral region, these involved

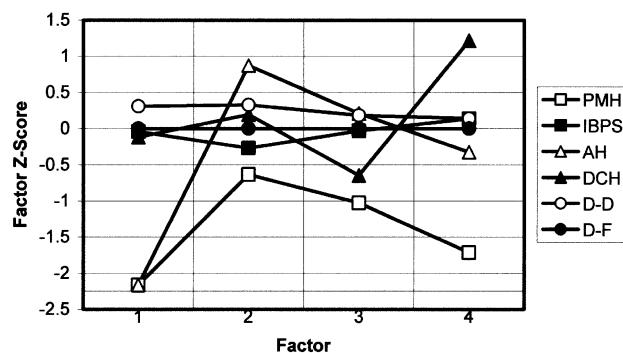


Fig. 10 Graph demonstrating the distribution of factor Z-scores for the six clinical groups. The factor Z-score was computed based on factor loading of the clinical signs on each of the four factors using the regression method and converted to Z-scores. The factor Z-score pattern was then analysed to highlight the major clinical characteristics of each group. Abbreviations as in text. Factor 1, strength; factor 2, cranial; factor 3, upper extremity dysmetria; factor 4, lower extremity dysmetria.

all basilar pontine regions including those situated particularly within medial parts of the descending peduncular (corticofugal) fibre bundle. Lesioned voxels were also in the median, paramedian and medial aspects of the ventral and peripeduncular nuclei in levels II and III.

Hand dexterity and strength

Hand dexterity correlated with lesions of pontine levels I and II, with less involvement of level III. Voxels were located in medial, ventral and intrapeduncular areas, and involved the ventral, paramedian, dorsomedial and medial aspects of the dorsal pontine nuclei, as well as the intermediate aspects of

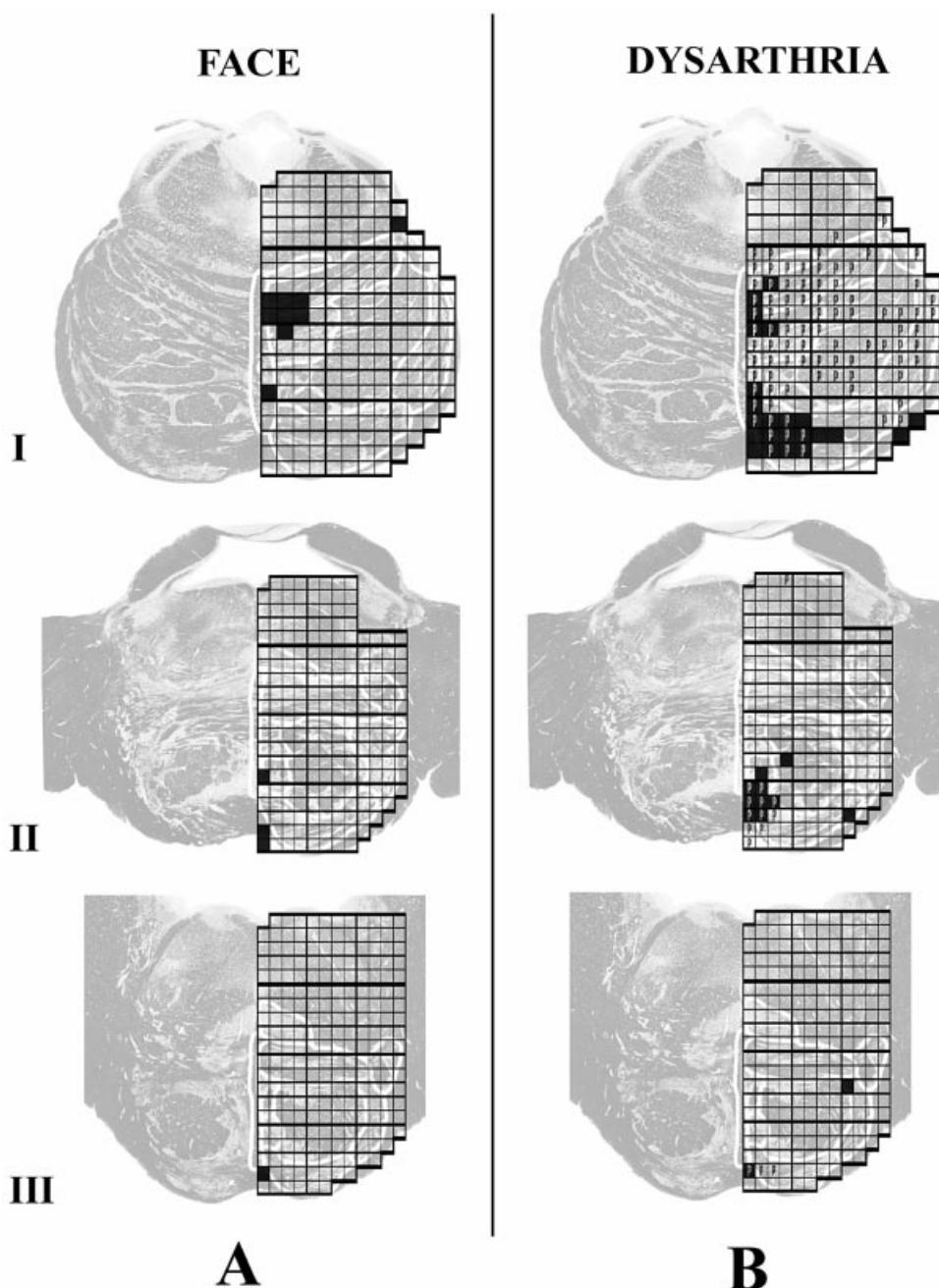


Fig. 11 Topographic maps of motor representations in the human basilar pons derived from correlation analysis of patients with pontine stroke. Pontine levels I–III are shown from rostral to caudal pons, as in Fig. 1A. (A) Face representation (shown in shaded black voxels) within the pontine nuclei. (B) Speech representation (shaded black voxels) in the pontine nuclei. The letter p denotes voxels that correlated with dysphagia.

the intrapeduncular and peripeduncular nuclei (Figs 12A and 14). Hand strength was located mostly in the middle of the peduncular fibres in level I, and was ventral in levels II and III in the peripeduncular, paramedian, ventral and lateral pontine nuclei. Whereas there was some overlap between hand dexterity and hand strength, there were a large number of voxels in levels I and II particularly, in which the two functions were anatomically distinct.

Upper extremity dysmetria

Arm coordination correlated with lesioned voxels mostly in level I, and to a lesser extent in levels II and III, with a medial and ventral preference (Figs 12B and 14). These voxels were situated most heavily in the ventral pontine nucleus, and in level I they were also present in the paramedian nucleus, lateral aspect of the dorsomedial nucleus, and the medial and intermediate parts of the intrapeduncular nucleus.

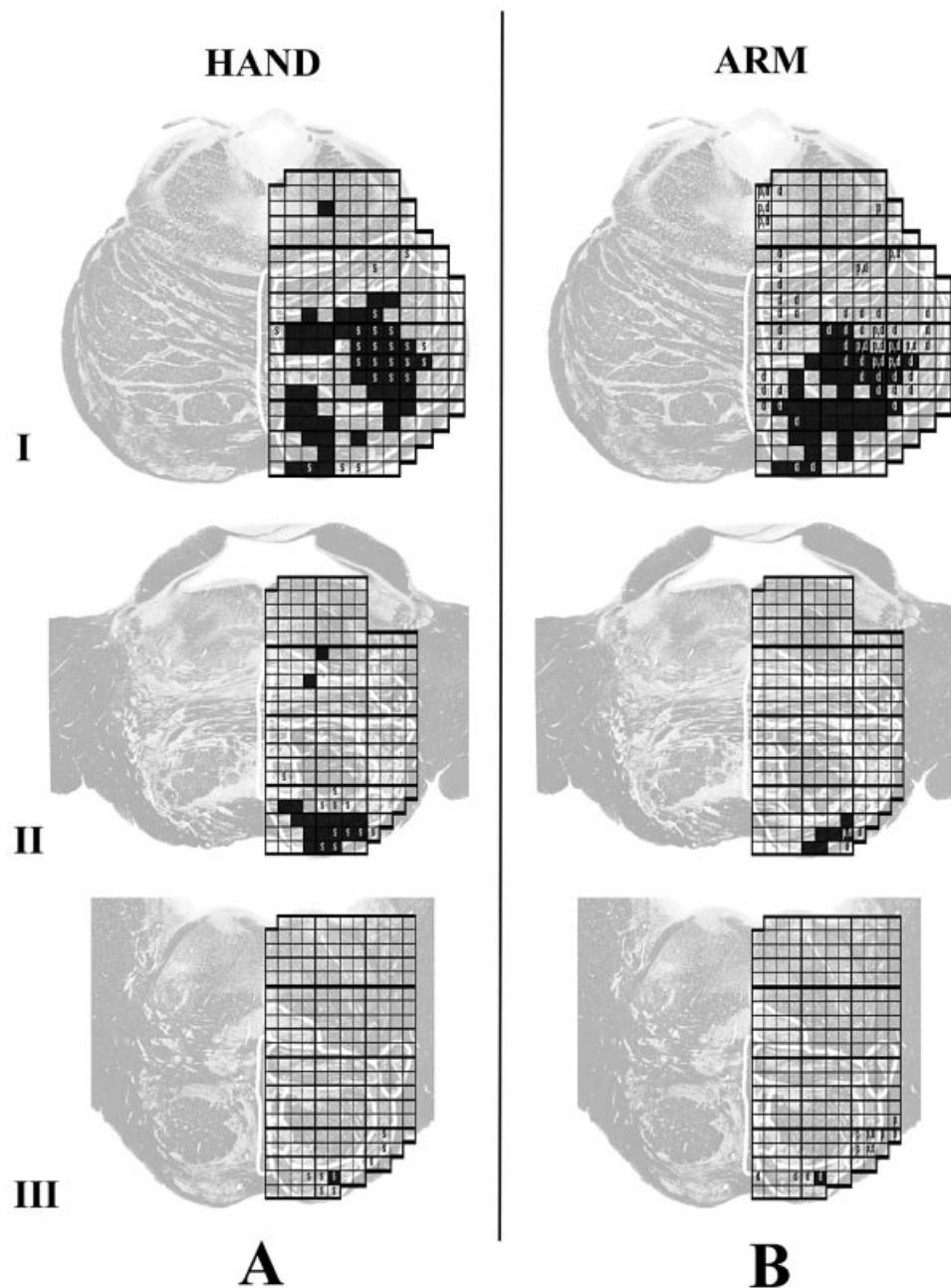


Fig. 12 Topographic maps of hand and arm representations in the human basilar pons. (A) Hand dexterity is shown in shaded black voxels and hand strength is denoted by the letter s. (B) Arm dexterity is shown in shaded black voxels and arm strength is denoted either as p for proximal (shoulder, elbow) or d for distal (wrist).

Upper extremity strength

The disparity identified in the hand between locations of voxels that correlated with strength versus those that were associated with dexterity was more pronounced for the arm, and further still for the leg. Upper extremity weakness correlated particularly with voxels in the middle and lateral parts of the descending corticofugal fibres in level I (Figs 12B and 14). Voxels were also present in a number of nuclei in level I, involving median, dorsal, dorsomedial,

paramedian, ventral and lateral nuclei as well as the nucleus reticularis tegmenti pontis (NRTP) and the medial part of the tegmentum. In levels II and III, arm strength voxels were in the ventral and lateral nuclei. Proximal (shoulder and elbow) strength was in more lateral regions of the corticofugal fibres and the dorsal and lateral nuclei, whereas distal (wrist) strength had a wider distribution as above. The medial tegmentum in level I correlated with both proximal and distal arm strength.

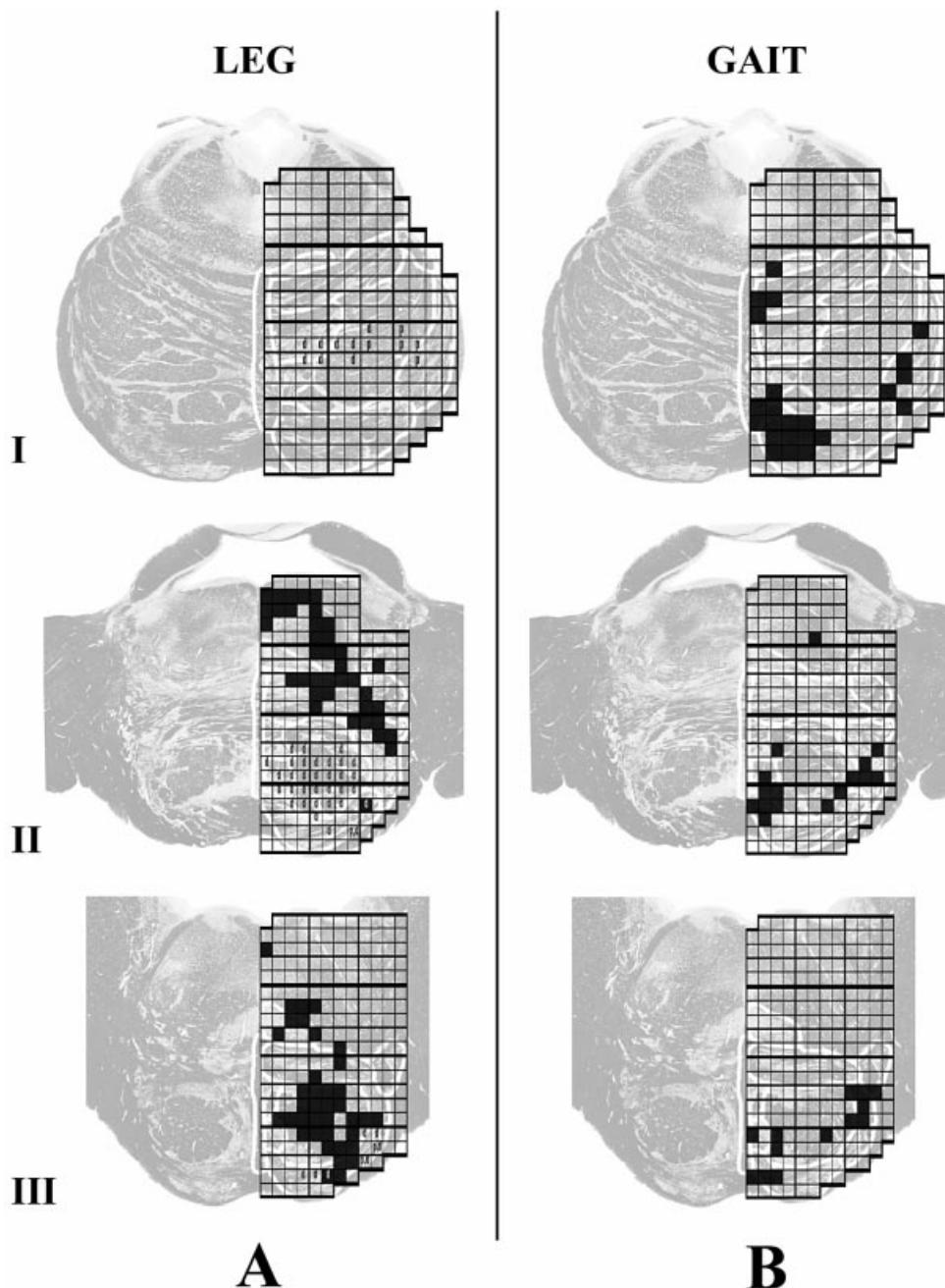


Fig. 13 Topographic maps of the human basilar pons to show the representations for the leg and gait. **(A)** Leg dysmetria is shown in shaded black voxels and leg strength is denoted by the letter *p* for proximal (hip, knee) or *d* for distal (ankle, toes). **(B)** Gait is shown in shaded black voxels.

Lower extremity dysmetria

Lower extremity dysmetria was correlated with lesions in the mid and caudal pons, with a more lateral distribution than those for the arm (Figs 13A and 14). Lesioned voxels were distributed in the lateral and dorsolateral nuclei, and lateral parts of the dorsal and ventral nuclei. The dorsal and lateral parts of the intrapeduncular and peripeduncular nuclei as well as the NRTP were involved in level III. Additionally, regions

that correlated with poor coordination of the leg were in the medial and intermediate parts of the tegmentum.

Lower extremity strength

Weakness of the leg was correlated with infarction in an entirely different group of voxels from those associated with lower extremity dysmetria. Voxels producing proximal (hip

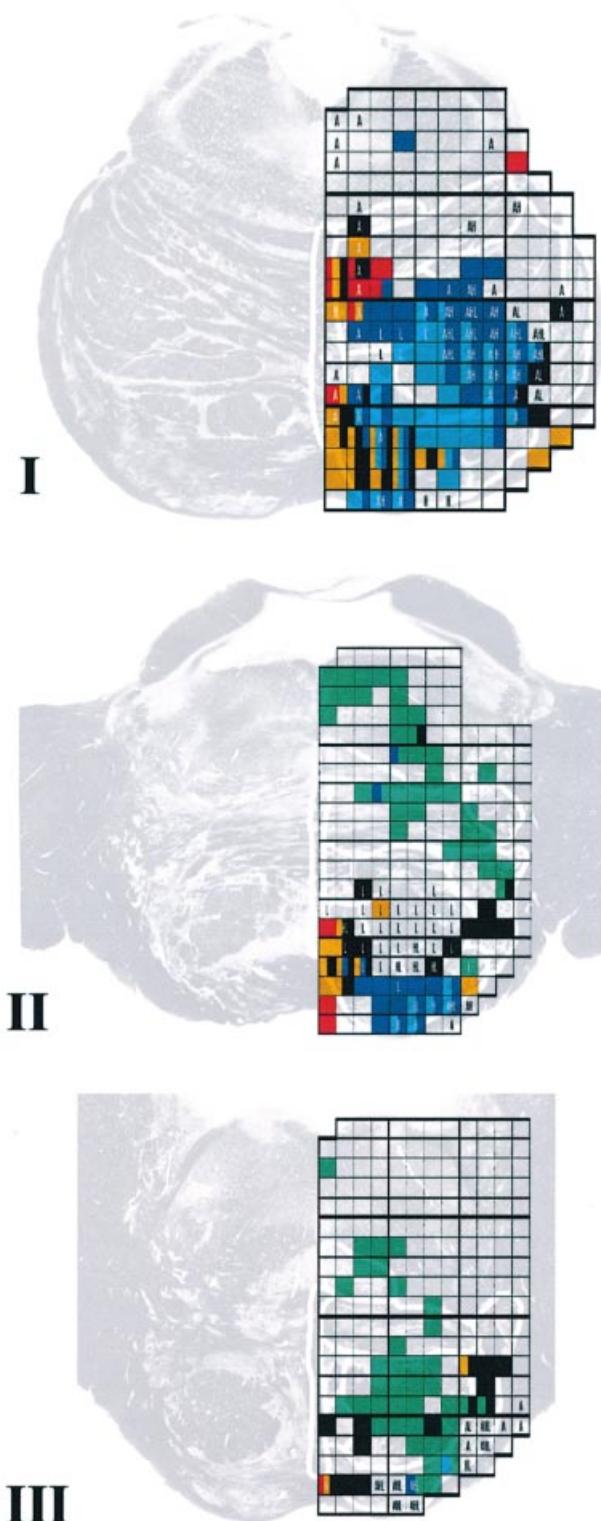


Fig. 14 Colour-coded composite summary diagram to illustrate the topographic map of motor representations in the human pons derived from analysis of basilar pontine stroke. Pontine levels I–III as above. Face, red; dysarthria, orange; hand dexterity, dark blue; arm dysmetria, light blue; leg dysmetria, green; gait, black. A = arm strength; H = hand strength; L = leg strength.

and knee) as well as distal leg weakness (foot) were located overwhelmingly within the descending corticofugal fibres in level II and to a lesser extent in level I (Figs 13A and 14). Scattered voxels in the lateral peripeduncular, lateral, ventral and paramedian nuclei also correlated with leg strength. Proximal leg strength was situated lateral to distal leg strength in the peduncle in level I.

Gait

Impairment of gait was correlated with voxels distributed in focal areas throughout pontine levels I–III, mostly within the nuclei rather than the corticofugal fibres (Figs 13B and 14). Most of the pontine nuclei were involved, in two major concentrations: one medial (median, dorsomedial, paramedian, NRTP, ventral, and medial part of the peripeduncular nucleus), and one lateral (lateral, and lateral part of the peripeduncular nucleus).

Other clinical features

Cranial nerve deficits (other than facial paresis, dysarthria and dysphagia)

Ipsilateral gaze paralysis and internuclear ophthalmoplegia were noted with tegmental lesions. Nystagmus was notably absent, except in two cases (7 and 24) with tegmental involvement. Ocular dysmetria was rarely noted (cases 13 and 21). Saccadic intrusion into pursuit eye movements was observed, but this was not a constant feature.

Deep tendon reflexes

Hyper-reflexia, usually with Babinski response, was present on the affected side in 19 patients. The plantar response was mute in one, reflexes were symmetric in three (cases 9, 16 and 8), and one was an amputee. Other signs of upper motor neuron dysfunction including Hoffman, Wartenburg and crossed adductor responses were variably present.

Sensory impairments

There were no instances of hemianesthesia. Paraesthesiae were present in the affected extremities in five patients at the onset of symptoms, but all modalities of sensation were normal. There was a mild decrease in appreciation of touch, pin and temperature in four patients with tegmental involvement (cases 5, 6, 8 and 20).

Higher order deficits

Motor neglect was apparent in two patients, in whom power was substantially better than spontaneous use of the limb suggested. Cognitive deficits included confusion at onset (cases 1, 9 and 24), but this was transient. Decreased arousal in case 2 may have been accounted for by transient

mesencephalic ischaemia resulting from basilar embolus. Depressed mood was clinically relevant in two patients (cases 4 and 24). Patient 1 had paraphasic errors, agrammatism and stuttering, and patient 21 with word-finding difficulty had decreased verbal fluency with testing, but neither had identifiable lesions outside the pons to account for these phenomena.

Ipsilateral dysmetria

Only cases 1 and 2 with PMH from the large pontine infarcts demonstrated dysmetria of the arm and leg on the side ipsilateral to the infarct. Cases 11 and 14 with AH had subtle overshoot with rapid finger following, but no other evidence of ipsilateral dysmetria.

Aetiology

Eighteen patients had risk factors predisposing to small vessel disease (hypertension, hyperlipidaemia, peripheral vascular disease, coronary artery disease, smoking, diabetes). In four of these patients, atherosclerotic changes, including severe stenosis, were also detected within the vertebrobasilar system. Embolic disease was implicated in four patients: focal filling defects in otherwise intact basilar arteries, atrial fibrillation, infarct in the pons simultaneous with central retinal artery occlusion, and patent foramen ovale with right-to-left shunt. One patient with colon carcinoma had no other evidence of hypercoagulability; one recently used inhaled and intravenous drugs; and one had risk factors for both cardioembolic and small vessel disease.

Prognosis

No patient succumbed to the pontine infarct. Case 23 died 2 years later from large vessel infarction and bronchopneumonia; case 4 died from intracranial haemorrhage with pathologically proven amyloid angiopathy 4 years afterwards. The two patients with PMH required care in a long-term facility. Recovery from the effects of the smaller lesions was generally rapid and good, although comprehensive follow-up data are not available.

Discussion

PMH

Fisher and Curry (1965) described PMH of vascular origin in 50 cases. Nine were studied pathologically, of which three were from unilateral lesions in the upper half or inferior half of the basis pontis. Patients had hemiplegia, severe dysarthria, and dysphagia. One case had difficulty gazing to the left, another had drowsiness and paranoid ideation, and a third had 'uncontrollable laughter of a remarkable degree' (p. 36).

AH

Fisher and Cole (1965) later described homolateral ataxia and crural paresis, the 'unusual neurologic deficit' in which the arm and leg on the same side show a combination of severe cerebellar-like ataxia and pyramidal signs. The ankle and toes were particularly weak. Patients were unable to walk unaided, or demonstrated circumduction of the leg as in 'ordinary hemiplegia', or lurching gait. In some, the affected hand felt 'swollen, stiff, larger, tight'. Articulation was impaired only rarely, and horizontal nystagmus was noted occasionally. The authors reasoned that the lesion could be in the internal capsule or basis pontis. If it were in the pons, it would be 'affecting both the pyramidal system and the pontine nuclei or their processes destined to cross to the opposite middle cerebellar peduncle ... but a clear example of this phenomenon has never been reported' (p. 53). In a subsequent clinicopathological report (Fisher, 1967), pathological lesions in AH were demonstrated at the junction of the upper one-third and lower two-thirds of the basis pontis.

DCH

Case 1 of Fisher's (1967) report had DCH from a lacune deeply situated in the most rostral left basis pontis. There was right central facial weakness, moderately slurred speech, intact power in the limbs, but right arm rapid alternating movements were clumsy, finger-nose testing was ataxic, and tapping the index finger on the thumb was slow and dysmetric. There was no leg dysmetria, and although gait was brisk he was unsteady and dragged the right leg, and the right plantar response was extensor. Fisher (1978) thought it 'best to regard this syndrome as a variant of ataxic hemiparesis'.

Subsequent analyses

A number of later reports described weakness and ataxia from pontine stroke (e.g. Van Gijn and Vermeulen, 1983; Koppel and Weinberger, 1987; Huang *et al.*, 1988). The definition of AH has been variable and confused with DCH, however, and the responsible lesion has been localized to the internal capsule, corona radiata and thalamus. Dysarthria is considered by many to indicate a pontine rather than a hemispheric cause of AH (Huang and Lui, 1984; Nighoghossian *et al.*, 1993; Moulin *et al.*, 1995; Gorman *et al.*, 1998), although in patients with PMH dysarthria does not always have localizing value (Melo *et al.*, 1992), and Urban *et al.* (1999, 2001) document a number of locations within the corticolinguinal pathways to account for dysarthria in association with hemiparesis, with or without dysmetria. Glass *et al.* (1990) concluded from their six patients that when clinical criteria for DCH are strictly applied, the lesion is sure to be in the paramedian basilar pons.

Kim *et al.* (1995) studied 37 patients with pontine lesions, and concluded that large lesions of paramedian caudal or

middle pons correlate with PMH, lesions of similar size in paramedian rostral pons produce DCH, and lesions causing AH are 'located variously' but tend to spare the pyramidal tracts.

All 27 patients with acute paramedian basilar pontine infarcts studied by Kataoka *et al.* (1997) had dysarthria. Hemiparesis with upper extremity predominance was recorded in 15, brachial monoparesis in four, and pathological laughter in three. Paramedian infarcts in 15 cases that extended from the base to the tegmentum produced hemiparesis, with horizontal gaze abnormalities and sensory dysfunction in some. Seven patients with paramedian tegmental infarcts had abnormalities of horizontal eye movement and sensory deficits.

Bassetti *et al.* (1996) considered the previous detailed studies of pontine vascular anatomy (Duret, 1873; Foix and Hillemand, 1926; Biemond, 1951; Gillilan, 1964; Duvernoy, 1978) and delineated anteromedial pontine arteries that supply the medial portion of the corticospinal tract and part of the medial tegmentum; and anterolateral pontine arteries that irrigate the lateral part of the corticospinal tract and medial tegmentum. In their account, large infarcts in the anteromedial and anterolateral territories result in severe contralateral face, arm and leg paresis, dysarthria and ataxia, and occasionally ataxia ipsilateral to the lesion; and smaller infarcts in the anterolateral territory produce mild motor dysfunction corresponding to the lacunar syndromes of PMH, AH and DCH.

In a study of 150 pontine stroke patients, Kumral *et al.* (2002) determined five main clinical patterns according to the territory of the infarcted vessels. These were the anteromedial syndrome (58%), i.e. motor deficit with dysarthria, ataxia, and mild tegmental signs; anterolateral syndrome (17%), i.e. motor and sensory deficits with tegmental signs; tegmental syndrome (10%), i.e. mild motor deficits with sensory, oculomotor and vestibular system features; bilateral pontine syndrome (11%), i.e. transient loss of consciousness, tetraparesis, pseudobulbar palsy; and unilateral multiple pontine infarcts (4%), associated with severe sensory-motor deficits and tegmental signs.

Limited clinical syndromes of DF (Hopf *et al.*, 1990; Kim, 1994), pure dysarthria and isolated facial paresis (Kim, 1994) have also been described following restricted pontine lesions.

Observations from the present analysis

We grouped the presentations of basilar pontine stroke into six syndromes based on the patterns of deficit. In addition to PMH, AH and DCH, we documented dysarthria with dysmetria in the absence of obvious weakness (DD), dysarthria with facial paresis with minimal weakness or dysmetria (DF), and a constellation we termed incomplete basilar pontine syndrome (IBPS) in patients with abnormalities of all motor functions tested but who did not fit the more restrictive categories.

These pontine syndromes reflect the differential pattern of involvement of the basilar pons. PMH is the 'end result' of the destruction of one half of the basilar pons: motor function is devastated on the contralateral side, and there is profound dysarthria and dysphagia. The IBPS includes substantial impairment in all motor functions, but is less severe than PMH. Lesions are sizeable, and involve at least two pontine levels and many basilar pontine regions (or 'nuclei'). In AH, the lesions may be quite restricted, and are localized in levels II and/or III in the central aspect of the basilar pons. DCH lesions are in basilar pons level I, adjacent to the midline at the ventral or dorsal aspects. DF lesions are confined to the median and paramedian pons in level I. DD cases have lesions located in dorsal and lateral parts of the pons in levels II and III.

These clinical distinctions notwithstanding, there was considerable overlap among the syndromes. They appeared to be distinguished by the relative intensity of the deficits, rather than by their absolute presence or absence. This is exemplified in the distinction of AH versus DCH, in that AH may have a trace of dysarthria along with the extremity deficits, and DCH also has gait ataxia and some arm dysmetria. Additionally, symptoms and signs often evolved, further blurring the distinctions. For this reason, in our analysis, motor findings were characterized only after the clinical presentation stabilized, usually within 2-3 days of onset.

Validity of the clinical signs

The validity of the six clinical groups was tested using ANOVA. There was no significant difference between groups for the presence of gait impairment, implying that pontine lacunes produce some difficulty with gait. The remaining clinical signs helped distinguish between the groups. *Post hoc* analysis of facial paresis and dysarthria underscored the validity of DF as a distinct group. It also confirmed that absence of dysarthria distinguished AH from the other pontine syndromes.

Factor analysis

Analysis of the clinical signs devoid of *a priori* hypotheses and not influenced by prior definitions of clinical groupings revealed that certain clinical features grouped together on the basis of statistical probability. This clustering into four different factors accounted for 88% of the variance of the presentations. Thus, strength of the arm, hand and distal leg, and the integrity of gait clustered together (factor 1), i.e. they were either impaired or preserved in the same direction in the same patients. Dysarthria, facial paresis and dysphagia (factor 2) occurred together. Dysmetria of the arm and dexterity of the hand (factor 3) clustered together, as did dysmetria of the leg and proximal leg (hip) strength (factor 4). The factor analysis thus demonstrated that certain functions were damaged as a group. By corollary, each factor should be

accounted for by a similar anatomic lesion. Further, the presence of more than one factor (cluster of signs) in a particular patient should be accounted for by a combination of lesions that produce each of the factors. This hypothesis was supported by the structure-function correlational analysis.

Structure-function correlation

The anatomical-clinical correlation provided the novel understanding that there is topographic organization of motor function within the human pons, and that each motor function is represented in multiple discrete sites at different rostral to caudal pontine levels (Figs 11–14). Pontine regions concerned with strength of the extremities are separate and distinct from those concerned with dexterity and dysmetria, particularly for the leg, but also for the arm, and to a lesser extent for the hand. Strength correlates with the descending corticofugal fibres destined for the spinal cord, whereas dysarthria, facial movement and hand dexterity, arm and leg coordination correspond to the basilar pontine neurons situated around the peduncular fibres traversing the pons. Face and speech are represented most medially in the rostral and mid-pons; upper extremity control is subserved by nuclei at the medial and ventral part of the upper and mid-pons; and leg coordination corresponds to nuclei that have a more lateral situation within the mid- and caudal pons.

These findings suggest that the human corticopontine projection is organized in a manner similar to that in the monkey, in which each cortical area projects to multiple, discrete sites within rostral to caudal levels of the pons, with topographic organization. The face is represented most medially, arm in a circumferential lamella mostly medial to and within the peduncle, and leg lateral to the peduncle (Nyby and Jansen, 1951; Brodal, 1978; Hartmann-von Monakow *et al.*, 1981; Schmahmann and Pandya, 1989, 1997a, b; Schmahmann *et al.*, 2004a).

The anatomic arrangement of the human basilar pons uncovered by the present study provides an explanation for the results of the factor analysis (the clustering of the different clinical signs). Focal infarction destroys discrete pontine areas devoted to select motor functions that are topographically arranged within the same 'neighbourhood'. Thus, face, speech and swallowing form one factor, because these functions are anatomically grouped in the medial part of the rostral pons. Hand dexterity and arm dysmetria are a factor because of their close proximity in pontine levels I and II. Leg dysmetria and proximal leg strength are a factor because they localize within the lateral and ventral parts of pontine levels II and III, including the intrapeduncular and peripeduncular nuclei. Strength of the arm and leg form a factor because they are adjacent in the intrapeduncular region in level I and the peripeduncular and ventral regions in levels II and III.

The topographic map also helps explain the six clinical groupings. Destruction of the entire hemipons devastates function (PMH), and defines the maximum extent of the basilar pontine syndrome. The incomplete syndrome, with

involvement of all areas of function (IBPS), results from lesions of various sizes involving part of the topographic representation of each motor function represented in the pons. Lesions in the mid-part of the pons (in axial section) produce AH because weakness results from damage to corticofugal fibres, and ataxia/dysmetria from involvement of neurons interspersed in the intrapeduncular, peripeduncular and ventral nuclei. Facial weakness and dysarthria in DF arise because of involvement of the topographically close representations of face and articulation in the most medial pons. The additional features of extremity dysmetria and hand clumsiness in DCH arise because of damage to the laterally adjacent regions concerned with hand dexterity and arm coordination. Dysarthria and dysmetria occur as an isolated presentation when leg, arm and face pontine nuclear regions (in the lateral and lateral parts of the ventral nuclei) are involved, but the descending corticofugal fibres are spared.

Lesions of the tegmentum, particularly in pontine level II, were associated with leg dysmetria. Lawrence and Kuypers (1968) drew attention to the role of the medial motor system in the tegmentum (conveying vestibular, reticular, rubral and interstitial projections to the spinal cord) for control of trunk and posture. Mitoma *et al.* (2000) noted that patients with medial tegmental lesions had ataxic gait, and those with pontine base and tegmental lesions had a combination of limb dysmetria and gait ataxia. The present observations are consistent with these findings, and provide further evidence that Kuypers' medial motor system is important for gait.

Cognition and affect in pontine lesions

Disturbances of cognition and affect were noted in patients with level I lesions. One had stuttering, paraphasic errors, agrammatism and perseveration, with impaired comprehension, naming and repetition. Another had anomia, circumlocution, poor semantic and phonemic fluency, and impaired verbal working memory. Motor neglect was apparent in two cases. Fisher mentioned behavioural irregularities following pontine infarction. Silverstein (1964) reported spontaneous laughing and crying, and confusion, disorientation and irrational behaviour in 13% of his series, but these may have involved thalamic ischaemia. Drake *et al.* (1990) described two patients with grandiosity, irritability, hyperactivity, and paranoid and religious delusions following ventral pontine infarction. Kim *et al.* (1994) reported DCH with paranoia, impulsivity, disinhibition and poor judgement. Pathological laughter and crying was observed by Kim *et al.* (1995), Bassetti *et al.* (1996) and Kataoka *et al.* (1997), and by Parvizi *et al.* (2001) in a patient with cerebellar deafferentation from infarction of the middle cerebellar peduncle and basilar pons. Inappropriate laughter at the onset of cerebral ischaemia (*fou rire prodromique*) has been described as the heralding manifestation of bilateral ventral pontine stroke (Wali, 1993) and paramedian basilar pontine stroke (Tei *et al.*, 1997; Assal *et al.*, 2000).

Cognitive impairments following rostral pontine stroke have been attributed to disturbed tegmental serotonergic systems (e.g. Assal *et al.*, 2000). It is also possible that these observations in our patients resulted from disruption of the pontine component of the cerebrocerebellar circuits that incorporate the association areas, and that are considered to be the anatomic substrates of the cerebellar contribution to cognition and emotion (Schmahmann, 1991, 1996, 1997). In monkey, the rostral pons is the recipient of projections from the prefrontal and anterior cingulate cortices involved in many cognitive operations (Vilensky and Van Hoesen, 1981; Schmahmann and Pandya, 1995b, 1997a), and it is involved in the voluntary expression of laughter (Wild *et al.*, 2003).

Pathophysiology of the AH syndrome

Fisher hypothesized that disruption of corticospinal pathways above the medullary decussation produces contralateral weakness, hyper-reflexia and Babinski sign; whereas damage to basilar pontine neurons or their axons produces cerebellar features because pontocerebellar fibres decussate in the pons to enter the contralateral middle cerebellar peduncle. No patient in our study demonstrated weakness ipsilateral to the stroke, and only the two with PMH had ipsilateral dysmetria. If damage to pontocerebellar fibres produces contralateral ataxia, then why is it that 'a unilateral pontine lesion, which should equally affect nuclei and crossing fibers, does not give bilateral cerebellar signs' (Glass *et al.*, 1990, p. 493). In our anatomical study in monkey (Schmahmann *et al.*, 2004b), pontocerebellar fibres from one side of the pons traverse the opposite hemipons, and disperse amongst numerous, widely divergent pontocerebellar fascicles before coalescing in the opposite brachium pontis. Together with the motor corticopontine projections that terminate in multiple discrete regions in the middle and caudal pons (Brodal, 1978; Hartmann-von Monakow, 1981; Schmahmann *et al.*, 2004a), this arrangement may account for the absence of ipsilateral dysmetria in all but the largest infarcts. In smaller lesions, sufficient numbers of pontocerebellar fibres from the intact hemipons escape damage as they bypass the lesion on their way to the cerebellum, thus preventing ipsilateral dysmetria. Damage to pontine neurons themselves is therefore necessary and sufficient to account for contralateral dysmetria in pontine infarction. Following massive hemipontine stroke, ipsilateral dysmetria represents a pontine disconnection syndrome, as envisaged by Geschwind (1965) for white matter lesions in the cerebral hemispheres, because of the total or near-total disruption of the decussating pontocerebellar fibres linking intact neurons of the contralateral pons with cerebellum ipsilateral to the pontine lesion.

Aetiology, prognosis, management

Little is known concerning the pathology of the blood vessels responsible for causing basis pontis stroke. Three principal pathophysiological mechanisms may have accounted for

infarction in this series. (i) Basilar artery branch occlusion (Fisher and Caplan, 1971; Fisher, 1977) consistent with the hypothesis of Fisher (1967, 1978) concerning the pathogenesis of lacunar disease, in some cases with concurrent basilar stenosis as reported previously (Silverstein, 1964; Kim *et al.*, 1995; Bassetti *et al.*, 1996). (ii) Pathology in intrinsic pontine arterioles. Interestingly, nine of the 14 patients with presumed small vessel disease (and no overt basilar artery abnormalities on neuroimaging) awoke from sleep with symptoms of stroke. (iii) Embolic lacunar disease may have been the pathophysiology in patients with known thromboembolic disorders. Outcome was generally good, although PMH had a slow and incomplete recovery. Management in each case was determined by the underlying cause.

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