SHORT REPORT

Midbrain infarction: associations and aetiologies in the New England Medical Center Posterior Circulation Registry

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Abstract

Most reports of midbrain infarction have described clinicoanatomical correlations rather than associations and aetiologies. Thirty nine patients with midbrain infarction (9.4%) are described out of a series of 415 patients with vertebrobasilar ischaemic lesions in the New England Medical Center Posterior Circulation Registry. Patients were categorised according to the rostral-caudal extent of infarction. The "proximal" vertebrobasilar territory includes the medulla and posterior inferior cerebellar artery territory. The "middle" territory includes the pons and anterior inferior cerebellar artery territory. The "distal" territory includes the rostral midbrain, thalami, superior cerebellum, and medial temporal and occipital lobes. Midbrain infarction was accompanied by "proximal" territory infarcts in four patients, and by "middle" territory infarction in 19 patients. Thirteen patients had associated "distal" territory infarcts, three of whom had occipital or temporal lobe infarcts. Only three patients had isolated midbrain infarcts. Cardioembolism (n=11), in situ thrombosis (n=9), large artery to artery embolism (n=7), and intrinsic branch penetrator disease (n=5) were the most common aetiologies. Bilateral infarction and accompanying pontine infarction were associated with the most extensive vertebrobasilar occlusive disease. Midbrain infarction was 10-fold more likely to be accompanied by ischaemia of neighbouring structures than it was to occur in isolation. Recognition of the different patterns of infarction may act as a guide to the underlying aetiology and vascular lesions.

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Midbrain infarction has received little recognition in the neurological literature. Isolated brain ischaemia at this site is uncommon,^{1 2}

although it may have been underrecognised before the MRI era.

Existing reports have concentrated on patients with isolated midbrain infarction. With the exception of one larger series² they have consisted of a few patients discussing clinico-anatomical correlations³⁻¹² rather than stroke aetiologies or mechanisms.¹³ We describe the associations of midbrain ischaemic stroke and illustrate the causative diseases found among a large series of patients with posterior circulation ischaemia.

Patients and methods

The patients were identified from the New England Medical Center (NEMC) Posterior Circulation Registry. This is a prospective database of patients with symptomatic ischaemic lesions in the vertebrobasilar territory established by neuroimaging. Emergency admissions and interhospital transfers (together 75%) and tertiary outpatient referrals (25%) are all represented within the Registry. A total of 415 consecutive patients were accrued between November 1986 and February 1997. All patients had been evaluated at the NEMC by one of three cerebrovascular neurologists (LRC, Dr D DeWitt, or the late Dr M Pessin). Patients were included in the current series if there was evidence of infarction within the midbrain on CT or MRI using standard axial sequences (T1, T2, FLAIR). Only patients with definite midbrain involvement were included, patients with infarcts limited to the pontomesencephalic or diencephalic-mesencephalic borders were excluded. Comprehensive neurological, neurovascular, cardiovascular, and haematological investigations were performed. All data in the NEMC Registry were documented contemporaneously with patient assessment.

Stroke mechanisms were determined according to strict criteria elaborated elsewhere¹⁴: large artery occlusive disease required the demonstration of occlusion or severe stenosis of the vertebral, basilar, or posterior cerebral artery (PCA) with infarction in the territory of the diseased artery. Cardioembolism required the demonstration of infarction within the territory of superficial, multiple, or single large arteries with the demonstration of a cardiac

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The brainstem viewed from its ventral surface showing the principal vessels of the posterior circulation. AICA=anterior inferior cerebellar artery; BA=basilar artery; ICVA=intracranial vertebral artery; PCA=posterior cerebral artery; PcomA=posterior communicating artery; PICA=posterior inferior cerebellar artery; SCA=superior cerebellar artery.

donor source on echocardiography or documented atrial fibrillation on electrocardiography. Large artery to artery embolism was diagnosed in the presence of a severely stenosed or occluded proximal artery with evidence of infarction in its distal territory. Branch penetrator disease was demonstrated by infarction limited to the territory of penetrating branch(es) without large artery or cardiac disease.

The extent of posterior circulation infarction was categorised according to its rostral-caudal distribution (figure).¹⁵ The "proximal" territory is supplied by the intracranial vertebral arteries and the posterior inferior cerebellar arteries (PICA) (the medulla and inferior cerebellum). The "middle" territory is fed by the caudal two thirds of the basilar artery (up to the superior cerebellar arteries (SCAs) and the anterior inferior cerebellar arteries (AICAs) (the pons and the anterior inferior cerebellum). The "distal" or "top of the basilar" territory is fed by the rostral basilar artery, SCAs, and PCAs (the midbrain, thalami, superior cerebellum, temporooccipital cortex).

Results

Thirty nine patients (9.4%) with midbrain infarction were identified (25 men, 14 women, mean age 52 years (range 5 to 87 years)). Thirty four patients were white, three were Asian, and two were black. Vascular risk factors included known hypertension (n=21), ischaemic heart disease (n=14), hyperlipidaemia (n=12), smoking (n=10), diabetes mellitus (n=9), and peripheral vascular disease (n=3). Ten patients had known high risk sources of cardioembolism. These were atrial fibrillation (n=5), atrial septal defects (n=2), akinetic left ventricular segments (n=2), and a mechanical

prosthetic aortic valve (n=1). There were no significant differences in demographics or vascular risk factors in the reported patients compared with other patients in the NEMC registry.

All patients had brain imaging (CT in 34, MRI in 35, both in 30). Neurovascular imaging was performed using extracranial duplex ultrasound in 20 patients, transcranial Doppler in 25, MR angiography in 21, and intra-arterial angiography in 18 patients. One of these modalities was employed in eight patients, two were employed in nine patients, three in 18 patients, and all four modalities in one patient. One patient died before vascular imaging. One patient with a "top of the basilar" syndrome and atrial fibrillation, and a further patient with an isolated midbrain infarct presumed due to branch penetrator disease did not undergo neurovascular studies. Transthoracic echocardiography (TTE) was performed in 23 patients and transoesophageal echocardiography in eight patients (three of whom had had prior TTE).

Four categories of patients were identified. Midbrain infarction was associated with "proximal" brainstem infarction in four patients. In each patient the pons was spared. In 19 patients it was part of a "middle" territory syndrome in which the most caudal involvement was the pons (n=18) or the anterior inferior cerebellum (n=1). Three patients had isolated midbrain infarction without other rostral or caudal involvement. In 13 patients midbrain infarction occurred as part of a "distal" territory syndrome. This group contained 10 patients with associated diencephalic involvement, and three patients in whom there was coexisting infarction in the temporal or occipital lobes in the distribution of the PCAs. In the "proximal" and "middle" groups, more rostral involvement was also seen involving the thalami (n=1 and 3, respectively), temporal or occipital cortex (n=2 and 3, respectively), or SCA territory (n=2 and 7, respectively). The table shows clinical findings, stroke mechanisms, vascular lesions, and outcome.

Eleven patients had bilateral infarcts. Ten of these had extensive occlusive disease of the basilar artery (n=6), or extracranial (n=4) or intracranial vertebral arteries (n=3). Four had tandem disease. The other patient died before neurovascular evaluation.

Eye movement disorders (72%), hemiparesis or tetraparesis (62%), and ataxia (56%) were the most common signs. Consciousness was impaired in 17 patients (44%) of whom six were in coma. Four of these had associated pontine infarction and two had coexisting thalamic infarcts. Sensory (15%) and visual field deficits (8%) were demonstrable in a minority of patients. Vertical (n=9) and horizontal gaze paresis (n=5) and internuclear ophthalmoplegia (n=6) were the most common ocular motor disorders. Vertical skew deviation (n=4), horizontal one and a half syndrome (n=2), convergence paresis (n=2), and bilateral ptosis (n=3) were also present. One patient had a fourth nerve palsy, and two patients had third nerve paresis as part of Weber's syndrome. In 22

Clinical findings, stroke mechanisms, large artery vascular lesions, and outcome among 39 patients with midbrain infarction in the NEMC posterior circulation registry

	Infarct distribution				Total (n=39) (%)	
	Proximal territory Midbrain plus PICA cerebellum or medulla (n=4 (10%))	Middle territory Midbrain plus pons or AICA (n=19 (49%))	Isolated midbrain (n=3 (8%))	Distal territory Midbrain ±thalamus ±PCA or SCA (n=13) (33%)		
Clinical signs						
Ocular motor	4	11	1	12	28	72
Motor	3	12	2	7	24	62
Ataxia	4	8	3	7	22	56
Somnolence	3	2	—	6	11	28
Coma	—	4	—	2	6	15
Sensory	1	3	—	2	6	15
Hemianopia	2	1	—	—	3	8
Mechanism						
Cardioembolism	1	5	1	4	11	28
Large artery thrombosis	—	7	—	2	9	23
Large artery embolism	1	2	—	4	7	18
Branch penetrator	—	2	2	1	5	13
Other	1	3	—	—	4	10
Unidentified embolism	1	0	—	2	3	8
Proven large artery vascular lesion						
ECVA stenosis	—	2	—	1	3	8
ECVA occlusion	1	2	—	1	4	10
ICVA stenosis	1	2	—	1	4	10
ICVA occlusion	—	—	—	1	1	3
Tandem EC and ICVA stenosis	—	—	—	1	1	3
BA stenosis	1	3	—	2	6	15
BA occlusion	—	7	—	—	7	18
PCA occlusion	—	—	—	2	2	5
Outcome						
Dependent	1	7	1	10	19	49
Independent	2	8	2	2	14	36
No deficit	1	1	—	1	3	7.5
Dead	—	3	—	—	3	7.5

BA, basilar artery; ECVA, extracranial vertebral artery; ICVA, intracranial vertebral artery; AICA, anterior inferior cerebellar artery; PICA, posterior inferior cerebellar artery; SCA, superior cerebellar artery; PCA, posterior cerebral artery.

patients, the clinical signs were specific to midbrain lesions.

Two of the patients with isolated midbrain infarcts had hemiataxia with mild hemiparesis, both were considered to have intrinsic branch penetrator disease. The third patient had undergone surgery for cyanotic congenital heart disease and developed hemiataxia and a fourth nerve palsy. Cardioembolism was the presumed aetiology.

The most common stroke mechanisms were cardioembolism (28%), large artery thrombosis (23%), large artery to artery embolism (18%), and intrinsic branch penetrator disease (13%). Presumed embolic sources remained undetermined in three patients, and in four patients other stroke mechanisms were invoked (coagulopathy associated with carcinoma and HIV, traumatic dissection, and migraine).

Acute therapy included heparin (n=16), warfarin (n=19), and aspirin (n=6). One patient had angioplasty of an intracranial vertebral artery stenosis, and one patient received intra-arterial thrombolysis to a basilar artery occlusion secondary to paradoxical embolism through an atrial septal defect. One patient with a large PICA territory cerebellar infarct required a temporary ventricular drain for hydrocephalus.

Three patients were in the paediatric age group (ages 5, 6, and 7 years). One patient developed a basilar artery occlusion within 24 hours of percutaneous valvoplasty for congenital pulmonary stenosis. Another developed a basilar artery thrombosis whose aetiology remained unexplained. Dissection of the basilar artery was proved by intra-arterial angiography after the third patient hit his head while on

a playground swing. All three patients survived, the last with only minor disability.

Discussion

The vascular supply of the midbrain includes penetrating branches from the basilar artery (paramedian mesencephalic arteries), precommunicating and postcommunicating segments of the PCA (peduncular perforating arteries), and contributions from the SCA and possibly the anterior and posterior choroidal arteries. It is therefore vulnerable to ischaemia from various sources.

The incidence of midbrain infarction is unknown. Unless specific (usually ocular motor) signs are present it may be difficult to identify clinically especially if there is associated infarction in neighbouring structures. In 17 of our 39 patients signs specific to midbrain lesions were absent. Recognition was helped little by CT, and only in the MRI era has an appreciation of its frequency developed.

In the Lausanne series² isolated midbrain infarction occurred in 8% of posterior circulation strokes (22 of 281 patients) and accounted for 2% of all ischaemic strokes. However, we identified only three patients with isolated midbrain infarcts out of 415 patients with posterior circulation ischaemic lesions (0.7%). Ascertainment bias prevents more than a broad comparison between the NEMC and Lausanne registries and in both series there is probably incomplete referral of patients with predominantly ocular motor deficits. Although the mean age of our patients was only 52 years, we consider our

results to be generalisable to the practice of most cerebrovascular neurologists.

According to our data midbrain infarction is at least 10-fold as likely to be accompanied by neighbouring ischaemic lesions than it is to occur in isolation. Most often it accompanies pontine infarction giving rise to a "middle" territory syndrome (49% of patients). Extensive embolic or thrombotic occlusive disease in the intracranial vertebral arteries or the basilar artery is the most commonly identified vascular lesion. This disease may extend or embolise more rostrally giving rise to additional diencephalic, PCA, or SCA territory infarction. Conversely, PICA or AICA to SCA collaterals may develop, thus bypassing downstream ICVA or basilar occlusive disease. All three fatalities were in this "middle" group with the most extensive disease.

With thalamic infarction it occurs as part of a "distal" or "top of the basilar" syndrome¹⁶ with or without more extensive infarction in the territory of the SCA or PCA (33%). Artery to artery or cardioembolism seem to be the most common pathogenic mechanisms, but localised atheroma of PCA origin may also cause thalamopeduncular syndromes.¹⁷

Involvement as part of a "proximal" territory syndrome is less common (10%). Infarction in the territory of the intracranial vertebral artery or PICA often arises due to recipient embolism or local atheroma. Lesions here can also act as donor sites of embolisation to more rostral sites.¹⁸

A further analysis from Lausanne indicated that multiple, remote infarcts occurred in 11% of patients with acute posterior circulation territory strokes, and 90% of these had a supratentorial component.¹⁹ Large artery disease (either in situ thrombosis or artery to artery embolism) was the most common aetiology. Our series is not directly comparable as we also included patients with confluent infarcts extending into the pons or thalami.

An embolic aetiology of infarction was postulated in 54% of our cases with cardioembolism exceeding large artery to artery embolism by 11:7. No established embolic source was found in three patients but the thoracic aorta was not routinely imaged. In situ large artery disease accounted for about one quarter of cases. As the NEMC Registry was developed in the clinical setting, there was no blinding of the clinicians to the results of investigations. This may have influenced conclusions about stroke pathogenesis according to personal experience, particularly in patients with more than one possible cause.

Impairment of consciousness was present in 44% of patients and this may explain the apparent lack of sensory (15%) or visual field (8%) deficits. Unilateral damage of the caudal mesencephalic tegmentum or rostral pontine tegmentum usually causes somnolence or drowsiness but bilateral lesions invariably result in coma.²⁰

In addition to the ocular motor disorders we noted isolated downgaze paresis,²¹⁻²³ vertical one and a half syndrome,^{5,24} and isolated fascicular third nerve paresis (which may

mimic an extrinsic "diabetic third")^{6,7} are described. Whereas paramedian midbrain infarcts are more likely to cause nuclear third nerve paresis, the more laterally placed fascicular lesions may be accompanied by contralateral hemiparesis (Weber's syndrome), ataxia (Claude's syndrome), or hemiparesis plus involuntary movements (Benedikt's syndrome). Although two patients with Weber's syndrome were present in this series, MRI showed accompanying, but clinically silent infarction in the thalamus in one patient and in the pons in the other.

We used a robust framework for considering ischaemia in the posterior circulation. Recognition of the patterns of infarction enabled a rational approach to elucidating the underlying vascular lesions and stroke mechanisms. The variety of diseases described here should encourage a focused search for a causal mechanism that includes the extracranial and intracranial circulation and the heart.

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