

Hypothalamic and myocardial lesions after subarachnoid haemorrhage

R. DOSHI AND G. NEIL-DWYER

From the Departments of Neuropathology and Neurological Surgery, Brook General Hospital, London

SUMMARY The hypothalamus and myocardium of 12 patients who had died after a subarachnoid haemorrhage, and of six patients who had died from other intracranial pathology were examined. Only in the patients who had died from subarachnoid haemorrhage were histological lesions found in both the hypothalamus and myocardium. The possible significance of these findings is discussed with particular reference to the sympathetic nervous system.

Increased and prolonged sympathetic activity in patients after subarachnoid haemorrhage (Tomomatsu *et al.*, 1964; Iliynsky and Astrakhantseva, 1967; Neil-Dwyer *et al.*, 1974) has been strongly linked with a variety of electrocardiographic (ECG) abnormalities occurring in this disorder (Cruickshank *et al.*, 1974). Although there is substantial indirect evidence to support this statement, direct evidence is scanty. Myocardial lesions associated with a subarachnoid haemorrhage have been well documented (Conor, 1969), and similar lesions have been produced in animals either by stimulation of the hypothalamus (Melville *et al.*, 1963; Zavodskaya *et al.*, 1972), or with the parenteral administration of catecholamines (Reichenbach and Benditt, 1970).

Hypothalamic damage in patients after subarachnoid haemorrhage has been well described (Crompton, 1963; Smith, 1963) while a variety of animal experimental work has shown that abnormal hypothalamic function can lead to myocardial damage and cardiovascular disturbances (Melville *et al.*, 1963; Greenhoot and Reichenbach, 1969; Zavodskaya *et al.*, 1972). As yet there has been no clinicopathological study establishing whether there is a correlation between hypothalamic and myocardial lesions occurring in subarachnoid haemorrhage, a requisite if the pathophysiology of this condition is to be understood.

Patients and methods

All patients were admitted into the Neurosurgical Unit at the Brook General Hospital between January and September 1975. The patients were divided into two groups, group 1 containing 12 patients who had died after a subarachnoid haemorrhage, and group 2, a control group of six patients who died from a variety of causes, all of which produced raised intracranial pressure. The necropsies in group 1 were consecutive.

Of the 12 patients in group 1, eight were female and four male, the age range was 21–66 years, and the clinical details are given in Table 1; in group 2 there were four female patients and two male, and the age range was 20–62 years. The majority of patients in the subarachnoid haemorrhage group followed a fairly typical clinical course with a fluctuating but deteriorating level of consciousness, varying blood pressures and pulse rates (Table 1). Electrocardiograms (ECG) were recorded in six cases (Table 1), and in five of these were considered to be abnormal.

Brains and hearts from the 12 cases of subarachnoid haemorrhage and six cases of raised intracranial pressure due to other causes were examined; of the 12 brains in group 1 (Table 2), three showed intraventricular haemorrhage; four brains contained intracerebral haematoma, and in three cases there was a combination of intraventricular haemorrhage and intracerebral haematoma; of the remaining two brains, cerebral infarction was present in one and no abnormality was seen in the other.

Three blocks were taken from each hypothalamus for paraffin sections: (1) at the level of the

Address for correspondence and reprint requests: Dr R. Doshi, Department of Neuropathology, Brook General Hospital, Shooters Hill Road, London SE18 4LW, England.

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Table 1 Summary of clinical data of 12 patients who died after subarachnoid haemorrhage.

Patient	Age (yr)	Sex	SAH to death (days)	Level of consciousness	Blood pressure mmHg	Pulse min ⁻¹	ECG	Operation
ML	66	F	7	Fluctuating → deep coma	130 ↔ 150 70 ↔ 90	60-90	Short PR interval. Long QTc, inverted T wave	None
JS	34	F	14	Initially fully conscious. Further haem. → drowsiness, coma	110 ↔ 150 70 ↔ 110	70-130	Peaked T wave. Inverted T in V4, 5, 6	None
MB	27	M	1	Unconscious → deep coma	200 110	50-60	—	None
MG	21	F	1	Unconscious → deep coma	150 100	90	—	None
DW	38	F	18	Postoperatively increasing drowsiness → deep coma	Post Op 140 ↔ 170 100 ↔ 110	70-90	—	Craniotomy, Right aneurysm clipped
DMc	57	M	8	Increasing drowsiness → deep coma	160 ↔ 210 100 ↔ 120	100-140	Peaked P wave. Short P-R interval	None
BV	60	M	5	Drowsy → sudden deterioration	150 90	70-80	—	None
JT	30	M	23	Postoperative increasing drowsiness → deep coma	130 ↔ 200 80 ↔ 100	80-150	—	Craniotomy, Aneurysm wrapped
VM	62	F	6	Increasing drowsiness → deep coma	150 90	60-80	Normal	None
DR	46	F	5	Increasing drowsiness → deep coma	160 ↔ 190 100 ↔ 110	60-100	Short P-R interval. Large U waves.	None
BC	47	F	5	Initially fully conscious. Further haem. → coma	130 ↔ 170 90 ↔ 100	70-100	Depressed S-T segments in V4-6. Large U waves	None
DB	54	F	5	Initially conscious. Further haem. → coma	140 90	60-80	—	None

Haem. = haemorrhage; SAH = subarachnoid haemorrhage.

Table 2 Summary of results of postmortem examination of brains and hearts of 12 patients who died after subarachnoid haemorrhage.

Name	Site of aneurysm	Other pathology in brain	Hypothalamus	Weight of brain (g)	Myocardium	Evidence of raised intracranial pressure
ML	Anterior communicating artery	Haemorrhage in left basal ganglia and intraventricular haemorrhage	Extensive hypothalamic infarct	330	Focal necrosis of muscle fibres with inflammatory cell infiltration	—
JS	Left vertebral artery	Blood in posterior horns of lateral ventricles	Perivascular haemorrhage	330	Focal necrosis of muscle fibres with inflammatory cell infiltration	—
MB	Right internal carotid artery	Haemorrhage in right temporal lobe	Distension of perforating vessels and ball haemorrhages	270	Focal necrosis of muscle fibres with inflammatory cell infiltration	++
MG	Arterio-venous malformation	Haemorrhage in right frontal lobe	Perivascular haemorrhage	300	Focal necrosis of muscle fibres with inflammatory cell infiltration	++
DW	Bifurcation of both internal carotid arteries	Haemorrhage in left temporal lobe and intraventricular haemorrhage	Perivascular haemorrhage	250	Necrosis of individual muscle fibres	+
DMc	Right middle cerebral artery	Haemorrhage in right frontotemporal region	Perivascular cuffing and microinfarct	560	Necrosis of individual muscle fibres	+++
BV	Anterior communicating artery	None	None	430	None	+
JT	Right middle cerebral artery	Infarction in territory of right middle cerebral artery	Perivascular cuffing and microinfarct	275	Focal necrosis of muscle fibres with inflammatory cell infiltration	+++
VM	Anterior communicating artery	Intraventricular haemorrhage	Perivascular haemorrhage	380	Necrosis of individual muscle fibres	++
DR	None	Haematoma in left Sylvian fissure	Distension of perforating vessels and ball haemorrhages	270	Necrosis of individual muscle fibres	++
BC	Right vertebral artery	Intraventricular haemorrhage	Perivascular haemorrhage	390	Focal necrosis of muscle fibres with inflammatory cell infiltration	+
DB	Left middle cerebral artery	Haemorrhage in left temporal lobe and intraventricular haemorrhage	Perivascular haemorrhage	250	Necrosis of individual muscle fibres	+

optic chiasm, (2) at the level of the tuber cinerium; and (3) at the level of the mammillary bodies. Blocks from the upper medulla oblongata were taken at two levels. The sections were stained with haematoxylin/eosin (H and E), haematoxylin/Van Gieson and Luxol fast blue/cresyl violet.

Results

In the hypothalamus, six of the 12 cases showed small perivascular haemorrhages and oedema of the surrounding tissues in the periventricular region including the paraventricular nucleus and the supraoptic nucleus. It was difficult to assess depletion of neurones but some of the neurones in the paraventricular nucleus were shrunken and

atrophic. In two cases there was distension of perforating vessels and vessels with small ball haemorrhages (Fig. 1) similar to those described by Crompton (1963). Another two cases showed marked oedema of the vessel wall involving the endothelial cells with perivascular cuffing by polymorphonuclear leucocytes in the paraventricular nucleus (Fig. 2). Microinfarcts in this region were demonstrated by the presence of fat granule cells and polymorphonuclear leucocytes. One of the cases with severe ECG abnormalities (ML) showed almost complete infarction of the hypothalamus (Fig. 3); in this case small foci of microinfarcts were also present in the thalamus. No hypothalamic lesions were found in one case (Table 2). Sections from the medulla oblongata did not reveal any abnormality.

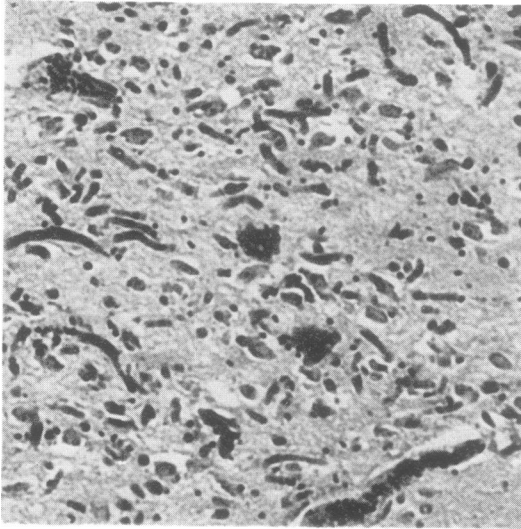


Fig. 1 Distension of perforating vessels with small ball haemorrhages in the paraventricular nucleus. (Haematoxylin and Van Gieson $\times 40$.)

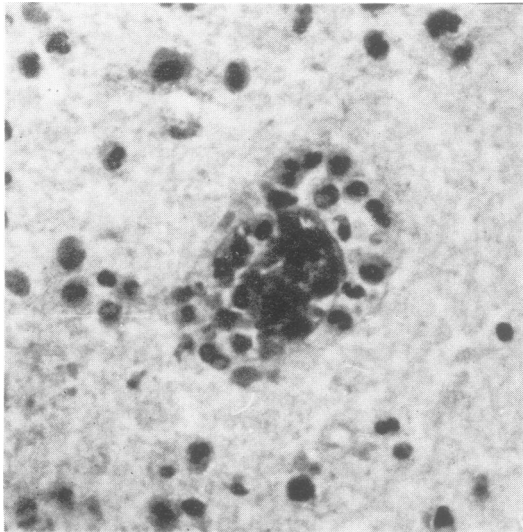


Fig. 2 Perivascular cuffing by polymorphonuclear leucocytes: note fat granule cells in the surrounding brain. (Haematoxylin and Van Gieson $\times 40$.)

CONTROL CASES

Of the six cases of raised intracranial pressure, three brains contained gliomas, two showed multiple metastases from carcinoma, and a massive subdural abscess was present in one.

Blocks from the hypothalamus and medulla were taken from these brains at the same level as the cases with subarachnoid haemorrhages, and



Fig. 3 Pale area in the right lower corner of the hypothalamus is infarcted. (Luxol fast blue and cresyl violet $\times 3.5$.)

the sections were stained by the same techniques. Histologically no abnormality was found in the hypothalamus or in the medulla oblongata in any of these brains.

HEARTS

In a majority of these cases the coronary artery appeared to be normal but there was a moderate degree of atheroma in three cases while in a fourth, severe atheroma was present. Four blocks were taken for paraffin sections from the left ventricle, one from each of the following areas: posterior wall; anterior wall; interventricular septum and apex. The sections were stained with H and E and haematoxylin/Van Gieson.

HISTOLOGY

In six of the group 1 cases there were small areas of necrosis of muscle fibres with interstitial infiltration by polymorphonuclear leucocytes and macrophages (Fig. 4). In five of the remaining six cases the myocardial fibres were distorted and widely separated from each other. In these cases there was necrosis of individual muscle fibres which showed loss of striation, increased eosinophilia, and granular cytoplasm; these necrotic muscle fibres were surrounded by macrophages. In one of these cases along with myofibrillar degeneration there were small areas of subendocardial haemorrhage. Only in one case was no abnormality seen (Table 2).

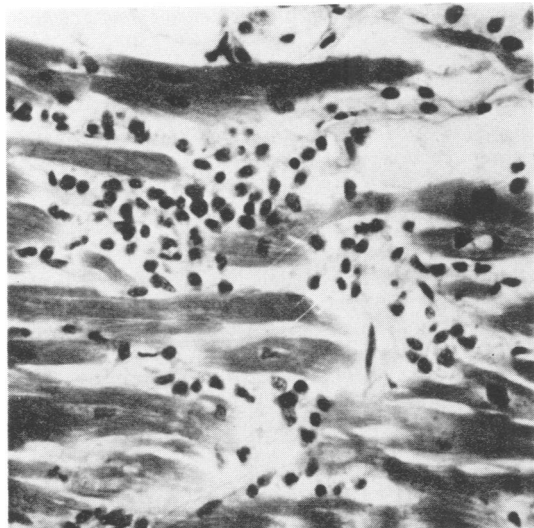


Fig. 4 Necrotic muscle fibre in the heart with interstitial inflammatory cell infiltration. (Haematoxylin and eosin $\times 100$.)

Hearts from the six control cases in group 2 were examined in a similar way but no abnormality of the muscle fibres was seen.

Discussion

Raised intracranial pressure has been suggested as a possible cause of the hypothalamic lesions (Crompton 1963) and ECG changes (Jachuck *et al.*, 1975) seen after subarachnoid haemorrhage. However, this study fails to support such an argument for, although in both groups there was pathological evidence of raised intracranial pressure, hypothalamic and myocardial lesions were found only in group 1 patients.

The clinical findings in these patients of a deteriorating level of consciousness, fluctuating blood pressures and pulse rates, and an abnormal ECG, have been associated with high blood levels of catecholamine after subarachnoid haemorrhage (Cruikshank *et al.*, 1974; Neil-Dwyer *et al.*, 1974). These high catecholamine levels have given support to the suggestion of increased sympathetic action after subarachnoid haemorrhage. One feasible explanation of this increased sympathetic drive is an abnormal hypothalamic response induced by spasm of the small vessels supplying the hypothalamus. Ischaemic lesions have been found at necropsy in the hypothalamus of patients who died after a subarachnoid haemorrhage. The action of the hypothalamus is two-fold: one, a direct action on the sympathetic nervous system

resulting in increased catecholamine production, and the other through the pituitary adrenal axis leading to high plasma cortisol levels. In addition, corticosteroids are known to have a potentiating action on the vascular effects of catecholamines (Selye, 1970). The effect of this on the heart, it has been argued, is to give rise to myocardial lesions and to ECG changes similar to those seen in subarachnoid haemorrhage.

This study demonstrates the coexistence of hypothalamic and myocardial lesions and adds further evidence to the above hypothesis. In all our cases, the lesions in the hypothalamus were bilateral and diffuse, with the major damage being in the periventricular region.

Although no definite site for sympathetic overactivity can be located in this study, there is evidence to suggest that the area surrounding the paraventricular nucleus may be responsible for such activity, though it is probable that the overall function of the hypothalamus is disturbed.

The type of cardiac myofibrillar degeneration, frequently focal and subendocardial, found in our cases has been well described not only in the hearts of patients who died after a subarachnoid haemorrhage, but also in association with pheochromocytomas and parenteral catecholamine administration (Reichenbach and Benditt, 1970).

In only one case in this study was there evidence of severe coronary artery occlusive disease but, as the myocardial lesions were patchy and occurred in a variety of sites in the left ventricle, coronary artery insufficiency due to atheroma was not a major factor.

In this preliminary study no cause and effect relationship can yet be established between abnormal hypothalamic action and the myocardial lesions sustained after subarachnoid haemorrhage. However, a case could be made for a controlled double-blind study on the action of prophylactic beta receptor blockade on these hypothalamic and myocardial lesions, and on the mortality of subarachnoid haemorrhage.

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