Clinicopathological study of neurological complications due to hypertensive disorders of pregnancy

AMANDA RICHARDS, DAVID GRAHAM*, ROSS BULLOCK

From the Departments of Obstetrics and Neurosurgery, University of Natal and Department of Neuropathology, Institute of Neurological Science, Glasgow, Scotland, UK*

SUMMARY Forty-three women with neurological complications secondary to eclampsia or severe pre-eclampsia were studied by CT scanning and in six intracranial pressure (ICP) monitoring was carried out. In seven women who died, neuropathological findings were correlated with clinical features. Cerebral oedema was present in 27 of the patients studied and the severity of oedema correlated to the duration of intermittent seizures. In five of the six women who had ICP measured, this was found to be transiently high. Intracranial haemorrhage was demonstrated in four of the 43 women, all of whom died. Hypoxic-ischaemic cerebral damage and fibrinoid necrosis were the most important neuropathological lesions identified. The management of neurological complications of eclampsia may be placed upon a more rational basis by an understanding of the mechanisms responsible for these lesions.

Neurological complications due to hypertensive disorders of pregnancy are the most common cause of maternal death from these disorders.¹⁻³ However, the pathogenesis of these complications, namely eclamptic seizures, coma, visual disturbances and localising neurological defects, remains poorly understood. The purpose of this report is to document the neuropathological findings of seven women dying from eclampsia or severe pre-eclampsia. These changes are related to clinical and CT observations in a larger series of 43 women with pregnancy-induced hypertension (PIH) and one or more of the above mentioned neurological complications. The pathophysiological mechanisms which may have led to these lesions are reviewed.

Patients and methods

All patients in this series were treated at King Edward VIII Hospital, a referral centre for Black Africans in the Province of Natal. Due to inadequate antenatal care, eclampsia still occurs in approximately 1% of pregnant patients referred to this hospital. During a study period of 14 months, 192 eclamptic patients were treated in relation to approximately 19,000 deliveries.

Address for reprint requests: Mr M R R Bullock, Department of Neurosurgery, Institute of Neurological Sciences, Govan Road, Glasgow, Scotland, UK.

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Criteria for the diagnosis of eclampsia were as follows:
(1) A diastolic blood pressure of 110 mmHg or more,
(2) 2+ or more proteinuria on urinalysis (Albustix),
(3) The occurrence of a seizure.

All patients were managed according to a standardised protocol,⁴ which included seizure and blood pressure control, intensive monitoring and cerebral CT when required. Termination of pregnancy was achieved by caesarean section or vaginal delivery as indicated. Where clinical status and CT findings suggested high intracranial pressure (ICP) monitoring⁵ was carried out in a neurosurgical intensive care unit with hyperventilation, mannitol, steroids and althesin infusion. Details of patient management are reported elsewhere.⁶ In those patients who died, and permission for necropsy was obtained, the brain or blocks of brain were retained for neuropathological evaluation after prolonged fixation in formol saline.

Results

Thirty-nine study patients underwent cerebral CT. In 27 evidence of brain oedema was present (table 1). Six of these patients underwent ICP monitoring, and in five, ICP was raised. Three patterns of cerebral oedema were demonstrated which, when correlated with duration of intermittent seizures experienced, patient recovery rate and measurement of ICP, tended to represent a spectrum of increasing severity (table 1).

Intracranial haemorrhage was identified on CT scan in four cases and in seven instances the cerebral CT scan was considered to be normal (table 1).

Table 1 Clinical details and CT scan findings in 39 patients with neurological complication due to hypertensive disorders of pregnancy

CT finding	Number of patients	Average age (yr)	Average parity	Mean duration of seizures (h)	Number of patients with elevated ICP
Oedema					
diffuse	5	23	1.8	9.6 (± 3.4)	3
watershed	9	18	0.4	5.8 (± 1.0)	2
occipital	13	20	0.2	3.3 (± 0.6)	—
Total	27	20.3	0.8	6.4	5
Haematoma	4	25	4.6	1.5 (± 0.8)	—
Diffuse hypoperfusion	1	20	0.0	0.2	—
Normal	7	26	1.4	1.0 (± 0.5)	—

Neuropathological findings in seven patients (five eclamptic and two pre-eclamptic patients) have been correlated with clinical status and CT findings in table 2. Seven major neuropathological abnormalities were demonstrated:

(1) Vasculopathy (fig 1), acute vessel wall damage as evidenced by plasmatic vasculosis and fibrinoid necrosis was found in three of the seven patients. Changes were limited to the cortical regions in cases 1 and 4, whilst in case 2 only the brain stem was involved. Fibrin thrombi occluding abnormal vessels were only seen in case 1.

(2) Perivascular microhaemorrhages were seen in three cases demonstrating vessel wall damage (fig 2). In case 4 there were multiple haemorrhages that ranged from 2 to 20 mm in size. This patient had a marked coagulopathy which appears to have exacerbated these haemorrhages.

(3) Perivascular micro-infarcts were identified only in case 1. Lesions were limited to the cortex and were

only seen in relation to damaged vessels.

(4) Oedema: pallor of staining and spongiosis were seen, not only in relation to micro-infarcts but also diffusely throughout the white matter of the posterior halves of the cerebral hemispheres. This feature was demonstrated in three cases and interpreted as oedema.

(5) Hypoxic ischaemic brain damage, as evidenced by the histological features of the ischaemic cell process,⁷ was present in five cases. In case 1 changes were limited to the cortex whereas in case 2 they were most marked within the arterial boundary zone between the distribution of the anterior and middle cerebral arteries. In contrast the damage was distributed diffusely in cases 3, 6 and 7. In the latter two cases laminar necrosis, maximal in cortical layers 3, 5 and 6 was a striking feature. This histological evidence of hypoxic damage⁷ is correlated with clinical episodes of hypotension and hypoxia in table 2.

(6) Intracerebral haemorrhage. Subarachnoid and

Table 2 Clinical CT and neuropathological findings in 7 patients dying with hypertensive disorders of pregnancy

Case	Age & parity	Duration of seizures (h)	CT findings	Significant clinical events	Neuropathological findings
1	20/P1	18	Diffuse oedema. Basal cisterns effaced	ICP markedly elevated (80 mmHg)	Vasculopathy Oedema Hypoxic-ischaemic damage cortex
2	18/P1	12	Not done	BP dropped to 60/0 following post-caesarean section sedation	Vasculopathy Oedema Hypoxic-ischaemic damage arterial boundary zone Subarachnoid haemorrhage
3	23/P1	Pre-eclamptic	Normal brain (4 h after cardiac arrest)	Cardiac arrest following administration of Magnesium sulphate	Diffuse hypoxic-ischaemic damage
4	35/P6	One fit	Large intraventricular bleed	Caesarean section revealed an abruptio placenta of 15 ml	Vasculopathy Subarachnoid and intraventricular haemorrhage
5	18/P0	Pre-eclamptic	Not done	Dihydralazine infusion resulted in profound hypotension	No abnormality*
6	18/P0	4	Occipital oedema	Cardiac arrest	Diffuse hypoxic-ischaemic damage
7	17/P0	6	Not done	Cardiac arrest	Hypoxic-ischaemic damage

*Limited material available for examination.

Fig 1 Vasculopathy, arteriolar lesion consisting of necrosis and thickening of the vessel wall demonstrated (Martius scarlet blue stain $\times 285$).

intraventricular haemorrhage were identified in case 4, both being extensions of multiple small intracerebral haemorrhages. A small amount of subarachnoid haemorrhage in the hypothalamic region was seen in case 2.

(7) Evidence of transtentorial herniation due to raised ICP was identified in case 1 as bilateral wedges of necrosis in the medial parts of the temporal lobes.⁸

Discussion

Cerebral haemorrhage^{9 10} and cerebral oedema^{6 11 12} have been demonstrated on both CT scan and at necropsy in relation to eclamptic seizures. However, these neuropathological lesions have not hitherto been related to the clinical status of the patient and no pathological mechanisms have been postulated to inter-relate these lesions with our new finding of extensive hypoxic-ischaemic brain damage.

Vasculopathy Our findings suggest that the basic pathogenesis of CNS lesions in eclampsia is due to acute hypertensive vascular changes (fig 3). Vessel

damage, or vasculopathy, demonstrated histologically in our patients was similar to those lesions found in hypertensive encephalopathy.¹³ Vasculopathy was not present in either of the two pre-eclamptic patients, but was found to be present in case 4 who had fitted only once (table 2). This suggests that vasculopathy develops either just prior to or with the onset of seizures. The extent of vessel damage, however, appeared to be proportional to the number of seizures experienced. Associated vascular thrombi were demonstrated only in case 1 who fitted intermittently for 18 hours.

Vessel wall damage occurring in acute hypertensive states is thought to be due to loss of autoregulatory capacity and "breakthrough" or over-stretching of vessel walls at mean arterial pressures (MAP) of over 140 mmHg.¹³⁻¹⁵ Worsening of vessel damage with recurrent seizures may therefore in part be explained by the fact that MAP rises considerably during each seizure.¹⁶ Animal studies have demonstrated blood brain barrier breakdown with extravasation of Evans Blue, a protein bound tracer, when "breakthrough" of MABP occurs.¹⁴

Fig 2 Perivascular microhaemorrhages (H&E stain $\times 285$).

The histological studies did not provide any evidence to suggest that vascular changes were localised to any specific regions of the brain. However, Govan¹⁰ commented that petechial haemorrhages appeared predominantly in the occipital lobes in eclamptic patients. In addition, there is experimental evidence in animals that a tendency exists for hypertensive vascular changes to be most prominent in the arterial boundary zones of the cerebral hemispheres.^{14 17 18} In an unpublished study of cerebral blood flow (CBF) in two eclamptics we have demonstrated increased CBF, most marked in the grey matter of the watershed or arterial boundary zone regions. We feel that this, plus the finding of cerebral oedema occurring predominantly in eclampsia in occipital and watershed areas supports the suggestion that cerebral vasculopathy develops in eclampsia as a result of hypertensive peaks and "breakthrough", which in turn results in dysfunction of the blood brain barrier and oedema formation (fig 3).

Intracerebral haemorrhages Large haemorrhages were not a common finding in our series of 43 patients (table 2). The pathogenesis of multiple small

haemorrhages (2–20 mm) demonstrated within the cortical ribbon in case 4 remains uncertain; however, in some, but not all haematomas examined, there was either a centrally placed or closely associated vessel with evidence of vasculopathy. In addition, this patient had a severe coagulation disorder as shown by blood investigations and an abruptio placenta, the multiple haemorrhages may therefore have been exacerbated by thrombocytopenia as part of a disseminated intravascular coagulation syndrome. Coagulation disorders have frequently been demonstrated in eclampsia.¹⁹ Minimal reactive changes were demonstrated in association with haemorrhagic lesions, thus confirming their short duration.

Cerebral Oedema was suspected histologically by the pallor of staining and spongiosis of the neuropil. Cerebral oedema was previously thought to be the cause of clinical pre-eclamptic symptoms such as headache, nausea, vomiting and visual disturbances. However, we were not able to demonstrate oedema formation, either histologically or on CT scan in pre-eclampsia, or in eclampsia until a significant number of seizures had been experienced. Therefore, it seems unlikely

responsible for brain damage in this condition. There is evidence in favour of a form of hypertensive encephalopathy.

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