Myelin basic protein immunoreactivity in serum of neurosurgical patients

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SUMMARY Patients admitted to the neurosurgical wards for the management of nervous system tumours, subarachnoid and intracerebral haemorrhage, head injury, spinal and peripheral nerve lesions, and other miscellaneous neurosurgical conditions, were studied by assay of serum immunoreactivity for myelin basic protein. Of 171 patients, 70% proved to have elevated myelin basic protein activity. In cerebral cases the extent of brain damage assessed by clinical methods appeared to correlate with the appearance of elevated serum myelin basic protein. In spinal and peripheral nerve cases no similar elevation of myelin basic protein was observed.

In the management of several common neurosurgical conditions, particularly in brain tumours, in subarachnoid haemorrhage and in head injury, it is often difficult to predict during the early phase the probable degree of permanent structural brain damage caused by the disease process and by the therapeutic operative neurosurgical intervention. It is known from previous work of the authors^{1,2} and others^{3,4} that nervous system specific antigens may be released by trauma, stroke and demyelinating disease and their immunoreactivity determined by sensitive quantitative radioimmunoassay (RIA) in serum. In this study an assessment has been made of the correlation between, on the one hand, the early clinical evaluation and the late clinical outcome, and on the other hand the serum levels of immunoreactivity for myelin basic protein. This has been done for several diagnostic categories of neurosurgical patient, including cerebral, spinal and peripheral nerve cases.

Patients

The patients studied were 171 cases admitted to the National Hospitals for Nervous Diseases for neurosurgical management. Fifty-three cases of intracranial tumour (13 cerebral gliomas, 14 pituitary adenoma, seven meningioma, four metastases and 15 of varied histological types)

29 cases of cerebrovascular accident (20 subarachnoid haemorrhage, nine intracerebral haematoma), 19 cases of head injury, 36 spinal cases, six peripheral nerve cases and 28 other miscellaneous cases were included. Fourteen healthy laboratory personnel were taken as controls. The mean age of the patients studied was 48.5 years (0-20 years, 2%, 21-40 years, 24%, 41-60 years, 53%, 61 years and over, 21%). Forty-nine per cent were males and 51% females. Eighty-four per cent of patients were submitted to neurosurgical operation, and the mean duration of their stay in the neurosurgical unit was 19 days (0-10 days, 24%, 11-20 days, 44%, 21 days or more, 32%). The controls consisted of 14 volunteers aged between 21 and 35 years, mean age 26 years, and composed of 60% male, 40% female. The study was performed with the approval of the Ethical Committee of the National Hospitals.

Clinical methods

Diagnosis was established by conventional clinical methods on the basis of presenting history, physical examination and special investigations, including neuroradiology as well as from operative or from necropsy findings. In patients with tumour, diagnosis of tumour type and grading was based upon histological examination of operative biopsy. Clinical grading of severity in patients with subarachnoid haemorrhage was classified into five grades, according to the classification of Botterell.⁵ The type of lesion in head injured patients was classified in four categories as extracerebral haematoma, mixed intracerebral and extracerebral haematoma, severe intracerebral damage without extracerebral haematoma and moderate intracerebral damage¹ and level of responsiveness was charted according to the Glasgow Coma Score.⁶

In all patients the clinical state on admission was classified within the categories, in coma (Glasgow grade 3-8), in vegetative state, conscious but severely disabled, conscious but moderately disabled or conscious and

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Table 1 Mean maximum serum myelin basic protein values after operation according to admission status and outcome

Outcome		1	2	3	4	N
Clinical state at admission						
1		53.8 ± 15.8	135.0 ± 30.0	0	12.0	
	N	3	2	—	1	6
2		83.0	87.0	0	0	
	N	1	1	—	—	2
3		23.0	58.5 ± 10.1	123.7 ± 30.0	81.8 ± 26.3	
	N	1	4	7	4	16
4		0	126.0 ± 74.0	80.9 ± 35.0	68.1 ± 8.6	
	N	—	2	12	23	37
5		65.0	75.0 ± 5.0	92.0	74.9 ± 9.9	
	N	1	2	1	63	67

Results expressed as ng/ml ± SEM. Clinical status (1–5) and outcome categories (1–4) defined in text.

slightly or non disabled. The outcome at discharge was specified as dead, severely disabled, moderately disabled or good.⁷

Laboratory methods

Serum was separated and deep frozen at –70°C within 24 hours of blood collection by venepuncture. Assay was performed between one and twelve weeks after serum collection. Serum myelin basic protein immunoreactivity was assayed by a competitive inhibition RIA by a previously reported method,⁸ but with slight modifications to the buffer system to improve sensitivity. The concentration of 30% bovine serum albumin used in the carrier protein buffers was reduced by one third, the concentration of calf thymus histone was left unchanged. Standard binding inhibition curves were used to calibrate the assay using authentic human myelin basic protein (given by Dr M Kies, National Institute of Health, Bethesda, or purchased from Calbiochem-Behring, Switzerland). The detection limit of the assay (mass of myelin basic protein giving 10% inhibition of binding of tracer) was equivalent to a serum myelin basic protein immunoreactivity of 2.5 ng/ml.

Initial blood samples were taken from patients as soon as possible after admission and before operation. Subsequent samples were taken, where possible, at intervals of two days or less and for up to ten days after surgery.

Results

In the control cases the myelin basic protein levels ranged from undetectable to a maximum of 17 ng/ml, with a mean value of 7.2 ng/ml. The mean maximum myelin basic protein immunoreactivity found in operated patients with different categories of clinical status by outcome at discharge is summarised in table 1.

Fifty-eight patients had craniotomy (for tumour, subarachnoid haemorrhage and head injury), 11 had posterior fossa exploration (for tumour), 12 patients had burrhole biopsy (for tumour or abscess), five patients had trans-sphenoidal hypophysectomy, 28 spinal surgery, four had trigeminal percutaneous radiofrequency coagulation and 12 other miscellaneous cases. As the table shows, one patient

admitted in a poor condition died and one patient admitted with very good clinical status also died. Of the 128 operated cases 52% arrived in good condition (admission status 5), and 71% were discharged with good outcome (outcome category 4).

The mean maximum serum myelin basic protein immunoreactivity in operated patients, after surgery and analysed by type of surgical procedure, is shown in table 2.

Most types of intracranial lesions requiring surgery were associated with an elevated myelin basic protein level before surgery and levels remained high after surgical intervention. Spinal and peripheral nerve cases did not have significantly elevated serum levels before or after surgery. There was a highly significant difference ($p = 0.001$) in levels of myelin basic protein reactivity between the intracranial categories of operated tumour and cerebrovascular accident cases and operated spinal, peripheral and other non-intracranial cases.

Discussion

The results suggest that cerebral damage associated with intracranial tumour and cerebrovascular accident, as well as head injury, can lead to significantly

Table 2 Mean maximum post-operative myelin basic protein level by operative category

Operative category	N	Mean myelin basic protein ng/ml
Craniotomy	58	94.4 ± 12.5
Post fossa craniectomy	11	85.5 ± 21.1
Burrhole biopsy	12	70.3 ± 5.9
Transphenoidal hypophysectomy	5	73.4 ± 20.9
Percutaneous trigeminal electrocoagulation	4	72.2 ± 39.0
Spinal	28	30.2 ± 5.7
Peripheral nerve	8	52.0 ± 21.1
Miscellaneous	12	44.0 ± 6.8
Overall mean		76.5 ± 6.1
Total N	128	

Results expressed in ng/ml ± SEM.

elevated serum myelin basic protein levels. However spinal and peripheral nerve lesions as well as other miscellaneous conditions not causing parenchymal brain damage, do not produce significantly raised levels of myelin basic protein immunoreactivity in the serum.

Myelin basic protein derived by homogenisation of normal human spinal cord or peripheral nerve may be detected by the RIA methods used in this study. The failure to find significantly increased levels of myelin basic protein immunoreactivity in serum of patients after spinal or peripheral nerve surgery may reflect the relatively small mass of nervous tissue affected in these neurological conditions which require such surgery when compared to the large mass of nervous tissue exposed to damage before or after operation in intracranial diseases requiring neurosurgical treatment. An alternative possibility is that the normal blood brain barrier is more extensively breached by intracranial lesions than by spinal ones, allowing detection of increased myelin basic protein immunoreactivity in serum.

Previous studies of serum myelin basic protein have indicated that in head injury and in cerebrovascular accidents not requiring surgery there is a correlation between maximum attained myelin basic protein and outcome. This study indicates that in cases of intracranial tumour and of subarachnoid haemorrhage serum myelin basic protein immunoreactivity is significantly elevated and measurement of levels may be a useful biochemical complement to clinical prognosis. Further work is required to determine the relationship between the profile of myelin basic protein level found in serial studies in the early phase of management of intracranial tumour and subarachnoid haemorrhage and the late outcome in individual patients.

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