Pre- and postoperative changes in serum myelin basic protein immunoreactivity in neurosurgical patients


Department of Neurological Surgery, Institute of Neurology, Queen Square, London, England

In 44 patients undergoing neurosurgical procedures for intracranial tumors, subarachnoid hemorrhage, or spinal and peripheral nerve lesions, serum myelin basic protein (MBP) immunoreactivity was measured preoperatively and serially in the first 10 postoperative days. The double-antibody radioimmunoassay method was used, with a detection limit of 2.5 ng/ml in serum. Clinical evaluation was carried out at admission and on successive days during the period of neurosurgical management; outcome was assessed later. In the early postoperative phase, there was a fall in MBP immunoreactivity in all groups of patients. In the groups with intracranial tumor and subarachnoid hemorrhage, there was a subsequent rise in MBP immunoreactivity before the end of the 10-day period, which was not found in the group with spinal and peripheral nerve lesions.

KEY WORDS • myelin basic protein • radioimmunoassay • brain antigen • subarachnoid hemorrhage • intracranial tumor

Myelin basic protein (MBP) constitutes approximately 30% of the total myelin-sheath proteins and is one of the best-characterized of the central nervous system (CNS) specific antigens. Over the past decade, several quantitative immunoassays have been developed to detect MBP and attempts have been made to correlate MBP immunoreactivity in serum and cerebrospinal fluid (CSF) with the degree of CNS damage produced in varying neurological conditions.

In this study, we examined the serial changes of serum MBP immunoreactivity in different groups of patients undergoing neurosurgery, using a sensitive radioimmunoassay (RIA) for MBP.

Clinical Material and Methods

Patient Population

This series included 44 patients who were admitted to the National Hospitals for Nervous Diseases for neurosurgical management. There were 17 males and 27 females, with a mean age of 48 years. Diagnosis was established by conventional clinical methods on the basis of presenting history and physical examination, and special investigations including neuroradiology. Diagnosis of tumor type was by histological examination of operative biopsy material.

Seven patients had subarachnoid hemorrhage (SAH), 21 had intracerebral tumors, and 16 suffered from various spinal conditions. The SAH’s were graded I to V according to the Botterell scale. The tumors were diagnosed as follows: eight gliomas, three meningiomas, six pituitary adenomas, and four miscellaneous intracerebral tumors. In the spinal lesion group, seven patients underwent laminectomy for disc protrusion, and three for canal stenosis; two underwent a decompression procedure for syringomyelia, two required dorsal root entry zone sections, one a cordotomy, and one surgical treatment of a myelomeningocele. The mean hospital stay, according to disease category, was 26 days for the SAH group, 25 days for the intracranial tumor group, and 20 days for the spinal lesion group. Six of the SAH patients, 14 of the tumor patients, and three of the spinal lesion patients received steroids during their treatment.

Assay Procedure

Blood samples were taken within 24 hours before surgery, within 48 hours postoperatively, and subsequently at 2-day intervals for the next 8 days. Serum was separated, divided into two aliquots, and stored, frozen at −75°C, within 24 hours of blood collection by venipuncture. Radioimmunoassay for serum MBP im-
Pre- and postoperative serum myelin basic protein (MBP) immunoreactivity levels in the three groups of patients in this study. Values are means ± standard error of the means for seven patients in the subarachnoid hemorrhage group (upper graph), 21 in the tumor group (center graph), and 16 in the spinal lesion group (lower graph).

Assay Precision and Detection Limits

To evaluate intra- and inter-assay variation, three serum sample standards were tested in 10 successive assays. The reproducibility of the results obtained indicated the intra-assay variability to be ± 5% and the inter-assay variability to be ± 8%. The mean limit of detection was 1.5 ng/ml. All samples from one individual were assayed in the same RIA run to minimize differences in MBP results due to RIA variations.

Results

Examination of the preoperative MBP levels showed that the mean values were similar in the three diagnostic groups, ranging from 33.0 to 36.0 ng/ml (Fig. 1). In all groups, the MBP levels dropped in the 2 days immediately after operation. The mean of the serum MBP levels in the spinal lesion patients stayed below the mean preoperative level for this group throughout the 10-day period. However, in the tumor group, mean MBP levels rose at 3 to 4 days postoperatively to levels greater than those found preoperatively. After the first 2 days the mean MBP levels in the tumor group remained around 50 ng/ml. In the SAH group the mean MBP levels rose approximately 4 days after those in the tumor group, reaching 60 ng/ml after 10 days.

Analysis of MBP data was performed on logged values (Table 1), and references to MBP levels in the present study are to log serum MBP levels. Statistical analysis of the data by repeated-measures analysis of variance indicates a difference between MBP levels by diagnostic group (p = 0.009) and against time (p =

* Human myelin basic protein was a gift from Dr. M. Kies of the National Institutes of Health, Bethesda, Maryland; rabbit CNS myelin basic protein was obtained from Calbiochem-Behring, Switzerland.

<table>
<thead>
<tr>
<th>Time of Assay</th>
<th>SAH Group</th>
<th>Spinal Lesion Group</th>
<th>Tumor Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>preop postop</td>
<td>1.557 ± 0.18</td>
<td>1.531 ± 0.08</td>
<td>1.521 ± 0.11</td>
</tr>
<tr>
<td>1-2</td>
<td>1.475 ± 0.16</td>
<td>1.279 ± 0.10</td>
<td>1.352 ± 0.13</td>
</tr>
<tr>
<td>3-4</td>
<td>1.309 ± 0.19</td>
<td>1.042 ± 0.10</td>
<td>1.713 ± 0.08</td>
</tr>
<tr>
<td>5-6</td>
<td>1.444 ± 0.24</td>
<td>1.257 ± 0.12</td>
<td>1.700 ± 0.07</td>
</tr>
<tr>
<td>7-8</td>
<td>1.718 ± 0.13</td>
<td>1.427 ± 0.10</td>
<td>1.670 ± 0.11</td>
</tr>
<tr>
<td>9-10</td>
<td>1.779 ± 0.11</td>
<td>1.202 ± 0.12</td>
<td>1.710 ± 0.10</td>
</tr>
</tbody>
</table>

* MBP = myelin basic protein. Values are means ± standard error of the means for seven patients in the subarachnoid hemorrhage (SAH) group, 16 in the spinal lesion group, and 21 in the tumor group.
Myelin basic protein in neurosurgical patients

A significant interaction between diagnostic group and time (p = 0.001) revealed that patterns of change in MBP levels over time were different in the three groups. Furthermore, analysis of covariance, using preoperative MBP as the covariant, showed a positive correlation between preoperative and postoperative MBP levels in individual patients, and that differences between the groups over time were preserved when the differences in individual preoperative levels were taken into account.

Discussion

One possible explanation for the similarity in preoperative MBP levels is the requirement in this study of a 10-day sampling period. Hence, patients who were in very poor condition on admission and who may have died within 10 days of admission or, conversely, patients who were “well” on admission and therefore left the hospital before 10 days had elapsed, are not considered here. We are therefore dealing with a select group of patients who had a similar clinical status on admission and who may therefore have been releasing MBP into their serum at a similar rate.

The immediate postoperative fall in MBP levels seen in all patient categories was unexpected and has not, to our knowledge, been recorded before. This fall is almost certainly the result of a number of complex biological interactions and not simply an effect of surgery, although Rem and co-workers, 13 studying the postoperative changes in various acute-phase serum proteins, showed that general anesthesia alone resulted in a 7% to 10% decrease in plasma concentrations of all proteins. This would not, however, explain the marked reduction in MBP immunoreactivity observed in our patients postoperatively. Previous work has shown a postictal rise in antigens in the serum in patients suffering head injury or cerebrovascular accident. 12, 16 Alling, et al., 1 found an elevated MBP level in CSF samples obtained immediately after surgery from 13 neurological patients, although preoperative MBP levels were not measured.

One possible reason for the initial decrease reported in this investigation could be that the patients studied may have been releasing MBP into their serum for days, if not weeks, prior to surgery and therefore may have primed their immune system to the MBP antigen. If this were the case, then the MBP released at significant levels into the circulatory system during and after neurosurgery may have been bound to specific antibodies, thus rendering it undetectable in the assay. Work carried out by Paterson, et al., 14 has indicated the presence of endogenous MBP in the sera of clinically well subjects, and the presence of circulating antibody to MBP. It may therefore be that the earlier MBP rise found in the tumor group can be explained by the saturation of an antibody response by the massive release of MBP during craniotomy. We suggest that, in the tumor group, MBP (and other breakdown products of myelin) continues to be released at the surgical site, thus leading to the plateau effect seen above.

On the other hand, part of the late MBP release in the SAH patients may be related to demyelination occurring secondary to ischemia induced either at the time of the ictus or during operation. This may then result in the gradual rise seen as antibody is saturated by the continual MBP release.

Administration of drugs may have had an effect upon the results. Approximately 75% of patients in the tumor and SAH groups were receiving steroids as opposed to 18% in the spinal lesion category. This may have contributed in part to the marked overall rise in serum MBP immunoreactivity in the tumor and SAH groups when compared with the spinal lesion group. In those two groups, the immunosuppressive effect of the steroids may limit any immunological response to brain antigens released. A further factor responsible for the low mean MBP levels in the spinal lesion group is that decompressive laminectomy does not lead to as much myelinated tissue damage as does craniotomy.

The present study demonstrates the need for obtaining preoperative serum samples to interpret a patient’s MBP results, because of the variation in individual baseline MBP levels and in order to determine the incremental effect of operation over that of the underlying disease process. We believe we have shown the importance of determining both pre- and postoperative MBP levels in the clinical evaluation of patient status. The study further raises interesting questions over the biological interactions of CNS tissue damage and the possible immunological responses induced after neurosurgical intervention.

Acknowledgments

We would like to thank Professor L. Symon and Mr. A. Crockard for allowing us access to their patients. We are grateful to Mr. A. Jeavons of the Computing and Statistics Advisory Centre, Institute of Neurology, for his advice and assistance.

References


Manuscript received July 25, 1983. Accepted in final form December 16, 1983.

Mr. Thomas and Mr. Hoyle were recipients of an M.R.C. project grant, and Dr. Seeldrayers was funded by the British Council.

Address for Dr. Seeldrayers: Department of Neurology, Erasmus Hospital, Free University Brussels, Brussels, Belgium.

Address for Dr. Moussa: Department of Neurological Surgery, Faculty of Medicine, Ain-Shams University, Cairo, Egypt.

Address reprint requests to: Nicholas R. Hoyle, B.Sc., Department of Neurological Surgery, Institute of Neurology, Queen Square, London WC1E 3BG, England.