Cerebrospinal fluid myelin basic protein in hydrocephalus

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Immunoreactive myelin basic protein (MBP) levels were measured in cerebrospinal fluid (CSF) samples taken from 57 patients with active hydrocephalus (age range 3 weeks to 60 years). Of these patients, 28 (49%) had elevated MBP values (> 4.5 ng/ml). Elevated MBP levels were found in 44% of patients with congenital hydrocephalus, 75% of patients with posttraumatic hydrocephalus, 80% of patients with normal-pressure hydrocephalus, and 83% of patients with porencephaly. Also associated with abnormal MBP levels was the ventricular size as measured by computerized tomography scanning ($\chi^2$: p < 0.05): 36% of the patients with small ventricles (ventricle:brain ratio 0 to 0.4:1) had elevated MBP in the CSF, whereas 61% of those with moderate ventricles (0.41 to 0.6:1 ratio) and 100% of those with large ventricles (0.61 to 0.85:1 ratio) had abnormal values. Only 33% of those with maximal hydrocephalus (0.86 to 1.0:1 ratio) had elevated MBP levels, perhaps because of dilution effects. In three patients in whom CSF was obtained simultaneously by ventricular and lumbar punctures, the ventricular fluid had a consistently higher concentration of MBP, suggesting a cerebral origin. It is concluded that active hydrocephalus produces significant periventricular demyelination, probably as the result of mechanical stretching.

Key Words: myelin basic protein, hydrocephalus, ventricular size

The presence of immunoreactive myelin basic protein (MBP) in the cerebrospinal fluid (CSF) of patients with active multiple sclerosis is well established. The test is not specific, however, and elevated MBP levels are seen in CSF specimens from patients with a variety of other neurological diseases. A common feature of these disorders is active demyelination, whether on an autoimmune basis or as the result of nonspecific destruction of white matter, as may occur in severe head injury or stroke.

Pathological studies have demonstrated periventricular loss of white matter in hydrocephalus, presumably the result of physical disruption of the white matter by the ventricular distension. In addition, studies of visual evoked response have suggested delayed conduction through the optic radiations in hydrocephalic children, and demyelination of the periventricular white matter might play a role in this as well. In an attempt to further define the role of demyelination in the pathophysiology of hydrocephalus, we have analyzed the CSF of hydrocephalic children and adults with active ventricular dilatation for MBP concentrations.

Clinical Material and Methods

Patient Population

This series includes 57 patients, ranging in age from 3 weeks to 60 years. The diagnosis of acute hydrocephalus was made either by computerized tomography (CT) or at surgery (elevated ventricular CSF pressure at shunt revision in a known hydrocephalic patient). Patients with known active infection of the central nervous system (CNS) or a clearly atrophic process were excluded from the study. This series included patients with hydrocephalus due to a number of specific etiologies (Table 1). Samples of CSF were obtained during active decompensated hydrocephalus, by either lumbar or ventricular puncture at the time of initial shunt placement or shunt revision. Patients with porencephalic or arachnoid cysts were included if CT scanning suggested mass effect and increased CSF pressure was noted at surgery. In three patients, CSF was obtained simultaneously by lumbar and ventricular puncture. Samples were then stored at −40°C until assay.

Assay of Myelin Basic Protein

The details of the assay have been described previously. Briefly, antisera were prepared by inoculating rabbits or sheep with human brain white matter emulsified with Freund’s adjuvant. The animals were bled at the time of onset of symptoms characteristic of experimental allergic encephalomyelitis, and sera were selected based on demonstrated reactivity with pooled CSF obtained from multiple sclerosis patients in exacerbation.
TABLE 1

<table>
<thead>
<tr>
<th>Condition</th>
<th>Positive MBP (≥ 4.5 ng/ml)</th>
<th>Negative MBP (&lt; 4.5 ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Percent</td>
</tr>
<tr>
<td>congenital hydrocephalus</td>
<td>7</td>
<td>44</td>
</tr>
<tr>
<td>myelomeningocele/Arnold-Chiari syndrome</td>
<td>3</td>
<td>20</td>
</tr>
<tr>
<td>postmeningitic hydrocephalus</td>
<td>1</td>
<td>20</td>
</tr>
<tr>
<td>posttraumatic hydrocephalus</td>
<td>3</td>
<td>75</td>
</tr>
<tr>
<td>normal-pressure hydrocephalus</td>
<td>4</td>
<td>80</td>
</tr>
<tr>
<td>postsubarachnoid hemorrhage</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>post-tumor resection</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Dandy-Walker cyst</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>porencephaly/arachnoid cyst</td>
<td>5</td>
<td>83</td>
</tr>
<tr>
<td>encephalocele</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Crouzon’s syndrome</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>total cases</td>
<td>28</td>
<td>49</td>
</tr>
</tbody>
</table>

For the assay, 0.05 ml of a concentrated assay buffer (2 M tris-acetate, pH 7.5, containing 10 mg/ml of histone) and an appropriate concentration of antiserum were added to 0.5 ml of CSF. The mixture was incubated for 1 hour at 37°C, then 15,000 counts per minute of basic protein/ml labeled with iodine-125 (125I, specific activity 10 to 20 μCi/μg) was added and the mixture was incubated for an additional 18 to 24 hours at 4°C. The antibody-MBP complex was precipitated with 0.5 ml of cold absolute ethanol. The pellet and supernatant were separated by centrifugation, and each was assayed for radioactivity. The percentage of 125I-labeled MBP was then determined. Results were either negative (less than 4.5 ng/ml) or positive (4.5 ng/ml or more).

Results

Sixty-seven CSF samples were obtained from 57 patients (aged 3 weeks to 60 years, mean 9 years). Fifty-nine of the samples were obtained from the ventricle or a supratentorial CSF-containing cyst at the time of initial shunting, shunt revision, or shunt tap. The remaining eight samples were obtained by lumbar puncture in patients with communicating hydrocephalus. In three patients, CSF was obtained simultaneously from both the ventricle and the lumbar subarachnoid space.

Thirty-eight (57%) of the 67 samples and 28 (49%) of the 57 patients studied were positive for MBP levels of more than 4.5 ng/ml (Table 1). Although the number of patients in each etiological group is small, congenital hydrocephalus, posttraumatic hydrocephalus, normal-pressure hydrocephalus, and porencephalic cysts under increased pressure seemed to be associated with high MBP levels, whereas fewer patients with hydrocephalus associated with myelomeningocele and postmeningitic hydrocephalus had elevated MBP levels. Of the 57 patients, seven were infants (less than 3 months of age). In this group, only two (22%) had elevated MBP concentrations (6.3 and 6.0 ng/ml).

No clear relationship was noted between CSF MBP and other CSF chemistry results in these patients. Most patients with elevated MBP values had normal or low CSF total protein concentration and normal or elevated CSF glucose levels. The MBP also appeared independent of CSF leukocyte and red cell counts for those patients in whom these were determined; three patients subsequently grew Staphylococcus epidermidis from the CSF samples from which MBP assays had been obtained, and in two of these the MBP was elevated. Cultures of CSF were negative in all other patients in whom they were performed.

In 40 patients, CT scans were carried out just prior to obtaining CSF samples. In these cases, measurement of the ventricular dilatation was accomplished by selecting the CT cut that showed the largest degree of ventricular enlargement, and then calculating the ratio of the transverse width of the frontal horns to the width of the brain in the same coronal plane. Degree of ventricular enlargement was then defined as small (ratio 0 to 0.4:1), moderate (0.41 to 0.6:1), large (0.61 to 0.85:1), and maximal (0.86 to 1.0:1). The level of MBP was examined in relation to ventricular size as determined from the CT scans (Fig. 1). In the group with small ventricles, four of 11 patients (36%) had elevated MBP. Of the 18 patients with moderate ventricular dilatation, 11 (61%) had increased MBP, and all eight patients with large ventricles (100%) showed abnormally increased MBP in the CSF. Of the three patients in whom the ventricles were maximally enlarged, only one (33%) had positive MBP findings. The relationship between CSF MBP levels and ventricular size was statistically significant ($\chi^2 = 8.79, DF = 3, p < 0.05$).
CSF myelin basic protein in hydrocephalus

When CSF MBP was plotted against the ventricular ratio, a quadratic curve in the shape of an inverted parabola was obtained by regression analysis (Fig. 2), with the maximal MBP concentration occurring at a ventricular ratio of 0.6:1 (A_o = -12.08, A_1 = 79.77, A_2 = -62.79, F = 2.39, p < 0.05).

Simultaneous lumbar and ventricular CSF samples were obtained in three patients with communicating hydrocephalus (Table 2). In all of these patients, the ventricular concentration of MBP exceeded that found in the lumbar CSF.

**Discussion**

Myelin basic protein is elevated in almost all patients with multiple sclerosis during an acute attack, and in approximately one-half of those with the chronically active form of the disease. In contrast, in a group of 626 patients with non-demyelinating neurological disease, all but six had less than 4 ng/ml of basic protein in the CSF. It has become clear in recent years, however, that a number of neurological diseases that are not strictly demyelinating are associated with the abnormal accumulation of MBP in the CSF. These include cerebrovascular disease, head injury, encephalitis, and some neurosurgical procedures. It is believed that some destruction of myelin does occur in these cases, and that because of the proximity of the site of myelin breakdown to the ventricular system, some of the breakdown products find their way into the CSF pathways. Our results suggest that active hydrocephalus should be included in this group. A single case of elevated MBP has been reported in a patient undergoing neurosurgery to relieve hydrocephalus. Our data showed that nearly one-half of 57 patients with active hydrocephalus have CSF concentrations of MBP in excess of 4.5 ng/ml, which suggests that this may be a more general phenomenon than has been reported previously.

In our three patients with simultaneous sampling of lumbar and ventricular fluid the concentration gradient favors a cerebral origin for the MBP. Pathological studies in animal models of hydrocephalus also suggest that breakdown occurs, particularly in the periventricular white matter. Furthermore, these studies have shown that the degree and extent of demyelination were commensurate with the size of the ventricles. We have also noted this in that the number of positive MBP determinations increased with the degree of ventricular enlargement, except for the "maximal hydrocephalus" group. In these cases, the relatively low MBP concentrations can be explained by dilution of the protein by the huge amount of ventricular water, or possibly by the fact that there is simply less myelin present in the thin cortical mantle in those patients. Only two of seven infants aged less than 3 months old had elevated MBP, and these had relatively mild elevations. Although myelination begins in fetal life, and MBP has been detected in premature human fetuses, it is not surprising that a young infant in whom brain myelination is not complete shows less evidence of demyelination with ventricular dilatation than an older counterpart.

At the present time, determination of MBP levels probably has little use in the clinical diagnosis of hydrocephalus, since this can usually be made without difficulty by physical examination and CT scanning. It is important to realize, however, that decompensated hydrocephalus can result in misleading values when MBP levels are obtained to rule out other diseases such as multiple sclerosis or chemotherapeutic drug damage to the CNS. It is interesting that the MBP level was elevated in four out of five adult patients with so-called "normal-pressure hydrocephalus." It is conceivable that the MBP concentration in the lumbar CSF could be shown to have clinical usefulness in predicting outcome with shunting in this difficult patient population, since cerebral atrophy is not associated with elevated MBP values. Further work will be required to establish this.

Finally, the demonstion of demyelination in hydrocephalus sheds some light on the condition. Hydrocephalus is one of the few rapidly reversible conditions encountered by the neurosurgeon, although full recov-
Demyelination may take several months. It is likely that demyelination accounts for at least some of the dysfunction occurring with hydrocephalus, and that remyelination explains some of the instances of recovery following shunting.

References


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