

Research Article

Clinical Value of the Measurement of Myelin Basic Protein in the Cerebrospinal Fluid of Patients with Idiopathic Normal Pressure Hydrocephalus

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Abstract

The clinical role of the myelin basic protein (MBP) measurement in the cerebrospinal fluid (CSF) for the evaluation of hydrocephalus has not yet been established. The purpose of this study was to examine the MBP value in the CSF in the ventricle and/or lumbar canal in adult patients with idiopathic normal pressure hydrocephalus. All MBP values from the lumbar and shunt valve punctures were within the normal range (<40 pg/ml). On the other hand, all MBP values from the ventricle CSF were high, ranging from 67 to more than 2000 pg/ml. The ventricle MBP concentration was increased following the clinical progression of the symptom in patients with hydrocephalus. Gait disturbance and incontinent were not observed for patients with low ventricle MBP values. Clinical improvement was mainly observed in the hydrocephalus patients with low ventricle MBP values. Therefore, the ventricle MBP value may become an index of the destruction of the cerebrum and predictor of clinical improvement following shunt surgery.

Keywords: biomarker, hydrocephalus, myelin basic protein, cerebrospinal fluid, shunt

Introduction

The diagnosis of hydrocephalus is made according to the clinical symptoms and imaging study findings. Some biomarkers in the cerebrospinal fluid (CSF) have been studied to diagnose hydrocephalus and evaluate the surgical indication and prognosis [1-9]. Most of these biomarkers are not commercially available or covered under general health insurance. Myelin basic protein (MBP) in the CSF has been shown to increase in variable myelin destructing pathologies, including cerebral infarction, contusion, and multiple sclerosis [10-12]. MBP in the CSF is available as a commercial diagnostic test and is covered under Japanese health insurance. Some studies have reported the diagnostic value of MBP in the CSF of patients with hydrocephalus [10,13,14]. However, the clinical role of the MBP measurement in the CSF for the evaluation of hydrocephalus has not yet been established. The purpose of this study was to examine the MBP value in the CSF in the ventricle and/or lumbar canal in adult patients with idiopathic normal pressure hydrocephalus (INPH) and investigate its diagnostic value compared with the clinical and radiological findings and the prognosis of the patient.

Patients and Methods

This study included 14 adult patients who were clinically diagnosed with iNPH in our hospital. The cohort included 6 males and 8 females, and ages ranged from 64 to 92 years. A ventriculoperitoneal shunt (VPS) was placed in all patients. The CSF was collected via a lumbar puncture for 6 iNPH patients, and a ventricle puncture during VPS in all patients. The CSF sample was immediately sent to SRL Inc. (Tokyo, Japan) for the measurement of MBP.

The iNPH symptom onset was determined to be the rapid progression of dementia, gait disturbance or urinary incontinence. A slow progression of these symptoms was not determined to be a hydrocephalus symptom, because we could not rule out other causes, including normal aging. Pre- and post-surgical cognitive functions were evaluated using the Hasegawa Dementia Scale-Revised (HDS-R). The HDS-R is a popular Japanese evaluation form to assess the cognitive function, which is similar to or better than the Mini-mental State Examination (MMSE) for the evaluation of the cognitive function [15,16]. Pre- and post-surgical ventricle sizes were evaluated using Evans' index in axial images obtained using brain computed tomography. The post-surgical symptoms and ventricle size were evaluated 2 months after surgery.

Results

All MBP values from the lumbar punctures were within the normal range (<40 pg/ml). All MBP values from the ventricle CSF were high, ranging from 67 to more than 2000 pg/ml (Table 1). In a few patients, a separate CSF sample was collected during a single ventricle puncture. These pairs of CSF samples demonstrated similar MBP levels. There were 6 cases in which both the lumbar and ventricle CSF were measured, and the ventricle MBP concentration was constantly higher than the lumbar MBP concentration. There was no correlation between the patient's age and ventricle MBP value. Also, there was no correlation between the symptom durations and ventricle MBP value (data not shown).

Table 1: The ventricle MBP value and pre- and post-surgical symptoms in iNPH patients

Age	Sex	Ventricle MBP pg/ml	Primary symptom	Gait disturbance	Urinary incontinent	HDS-R	Evans index
88	F	67	dementia	+/-	-/-	8/10	0.32/0.23
70	M	108	gait	+/-	-/-	16/18	0.36/0.37
82	F	196	incontinent	-/-	+/-	18/24	0.39/0.37
79	F	232	gait	+/-	+/-	14/24	0.34/0.27
92	F	299	gait	+/-	+/-	NA	0.31/0.33
79	F	322	dementia	+/+	-/-	10/14	0.29/0.29
66	M	1080	gait	+/-	-/-	NA	0.31/0.32
75	M	1090	gait	+/-	+/+	11/20	0.43/0.30
64	M	1550	gait	+/-	+/-	28/29	0.37/0.35
72	M	>2000	gait	+/-	+/-	NA	0.37/0.37
84	F	>2000	gait	+/-	+/-	24/29	0.34/0.33
84	F	>2000	gait	+/-	+/+	27/28	0.29/0.22
78	M	>2000	dementia	+/+	+/+	9/17	0.38/0.34
75	F	>2000	gait	+/-	+/-	25/28	0.31/0.25

Among 14 iNPH patients, the primary symptoms were dementia for 3, gait disturbance in 10 and incontinence in 1 (Table 1). No correlation between the primary symptom and ventricle MBP value was found. Gait disturbance was not observed only one patient with relatively low ventricle MBP value. Incontinence was not observed for 4 patients.

The patients with incontinence showed statistically higher ventricle MBP values than the patients without incontinence (Mann-Whitney test, $p < 0.01$).

All shunt surgery was clinically effective. The post-surgical HDS-R showed improvement compared with the pre-surgical HDS-R, except for one patient those HDS-R was not fully evaluated. The pre- and post-surgical HDS-R and the level of improvement of the HDS-R was compared with the ventricle MBP value, however, no correlation was observed (Table 1). Post-surgical Evans' index was decreased compared with pre-surgical Evans' index, except for in 2 patients where it was nearly stable. Pre- and post-surgical Evans' index and the level of improvement of Evans' index were also analyzed, however, no correlation between these values and the ventricle MBP concentration was observed (Table 1). Two months after shunt surgery, the gait disturbances were improved in most patients except 2 patients, these 2 patients showed relatively high ventricle MBP values. The urinary incontinence was improved in 7 patients and not improved in 3 patients. These 3 patients showed relatively high ventricle MBP values (Table 1).

Discussion

The MBP concentration in the CSF has been investigated in various neurological disorders. Thomas et al. reported a significant elevation of the MBP concentration in the CSF immediately after head injury, which was related to the prognosis [17]. Lowenthal et al. reported that the MBP level in the CSF reflects the demyelinating disease activity, including inflammatory and vascular diseases [18]. Clinical improvement after shunt surgery was mainly observed in hydrocephalus patients with low ventricle MBP values. Thus, the ventricle MBP value may predict the clinical improvement of shunt surgery. According to our results, the ventricle MBP appears to represent the level of normal brain destruction.

Sutton et al. reported MBP levels in the CSF from various hydrocephalus patients, including congenital hydrocephalus, myelomeningocele, and arachnoid cyst [13]. Most CSF samples were obtained from the ventricle or supratentorial CSF-containing cyst at the time of surgery. In 5 NPH, four patients showed increased MBP levels in the CSF. In their MBP assay, a value greater than 4.5 ng/ml was determined to be positive. Although their measurement method and cut-off value of MBP in the CSF was different from our study, similar trends were observed. In their study, abnormal MBP concentrations in the CSF were highly observed in acquired hydrocephalus, but not in congenital hydrocephalus. Simultaneous lumbar and ventricle CSF sampling was performed in 3 patients. The ventricle MBP level was constantly higher than the lumbar MBP level. This result is consistent with our findings. The authors concluded that periventricular demyelination, as the result of mechanical stretching, is the cause of high MBP concentrations and accounts for the dysfunction of hydrocephalus.

Longatti et al. also reported raised MBP concentration in the CSF of 17 hydrocephalus patients [10]. Their study cohort had preoperative MBP levels in the CSF ranging from 9.93 to more than 100 ng/ml. After shunt surgery, the patients' MBP concentrations significantly decreased. Although the authors demonstrated that the MBP levels in the ventricle were constantly higher than that in the lumbar, the data they showed did not indicate the origin of the CSF. If the authors had compared the preoperative ventricle MBP and postoperative lumbar MBP levels, the decrease of the MBP concentration in the CSF would most likely not be determined to be an effect of surgery. Evans' index was not correlated with the MBP values. The authors concluded that Evans' index is a sign of previous cerebral damage, and MBP is an index of ongoing cerebral damage. Their conclusion coincided with our results, which showed that Evans' index was not related with the clinical prognosis. However, both previous studies [10,13] did not analyze the relationship between the ventricle MBP concentration and the symptom duration or clinical improvement. Thus, our study is the first to demonstrate the clinical significance of the ventricle MBP value, which is related with the symptom and may be a prognostic determinant of the clinical improvement after shunt surgery.

According to our findings, the lumbar MBP value was constantly lower than the ventricle MBP value. These results were similar to the previous reports [10,13]. If the release of MBP from the brain is continuous, the MBP value in the CSF space should be constant, as the protein and glucose values are stable in the CSF space. Our results suggest the intermittent release of MBP into the CSF during hydrocephalus. This should be verified by future studies. Albrechtsen et al. investigated the glial fibrillary acidic protein (GFAP) concentration in the CSF of NPH patients [19]. In all cases, the ventricle GFAP concentration was higher than the lumbar concentration. The authors concluded that high GFAP concentrations in the CSF of NPH patients were not due to the general impairment of the clearance of protein from the CSF, because the mean CSF albumin concentration was normal. This result supports the hypothesis of the active release of GFAP into the ventricle CSF during hydrocephalus.

McGirt et al. investigated the clinical course of 132 iNPH patients [20]. Gait impairment as the primary symptom and a shorter duration of symptoms predicted clinical improvement. Evans' index was not correlated with the shunt response. In our study, lower ventricle MBP level were correlated with the shunt response, while the primary symptom and Evans' index were not correlated. In our study, the primary symptom was not related to the shunt response, although our small sample size may not have allowed us to accurately determine this relationship.

In our study, the lumbar CSF was not valuable for the evaluation of hydrocephalus. Although a lumbar puncture is a routine clinical examination, a ventricle tap is not a routine examination. Therefore, more sensitive examination methods to measure the MBP in the lumbar CSF or a more sensitive biomarker should be determined by future investigations.

This study is associated with several limitations. The normal value of MBP in the CSF from a lumbar puncture is determined to be lower than 40 pg/ml in our study. We do not have any data regarding the normal value of MBP in the cerebral ventricle. This issue should be investigated by future studies. Additionally, we did not observe a significant correlation between the ventricle MBP level and the dementia scale or ventricle size. This result may be due to the small sample size of our study, therefore, these correlations should be investigated in a future large study, although a previous study also showed that Evans' index did not reflect the prognosis [20]. Lastly, we performed cross-sectional MBP measurements. We did not have longitudinal MBP data during the clinical course or after shunt surgery. Therefore, a longitudinal study should be planned.

Conclusion

The ventricle MBP concentration was increased following the clinical progression of the symptom in patients with hydrocephalus. Gait disturbance and incontinent were not observed for patients with low ventricle MBP values. Clinical improvement was mainly observed in the hydrocephalus patients with low ventricle MBP values. Therefore, the ventricle MBP value may become an index of the destruction of the cerebrum and predictor of clinical improvement following shunt surgery.

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