Influence of interleukin-6 on the development of peritumoral brain edema in meningiomas

Laboratory investigation

KYUNG-JAE PARK, M.D.,1 SHIN-HYUK KANG, M.D., PH.D.,1 YANG-SEOK CHAE, M.D., PH.D.,2 MI-OK YU, M.S.,1,3 TAI-HYOUNG CHO, M.D., PH.D.,1 JUNG-KEUN SUH, M.D., PH.D.,1 HOON-KAP LEE, M.D., PH.D.,1 AND YONG-GU CHUNG, M.D., PH.D.1

Departments of 1Neurosurgery and 2Pathology, Korea University Anam Hospital, College of Medicine; and 3School of Life Sciences and Biotechnology, Korea University, Seoul, Korea

Object. Peritumoral brain edema (PTBE) is associated with perioperative neurological deficits in patients with meningiomas. However, the pathogenesis of meningioma-associated edema remains unclear. In the present study, the authors investigated the expression of interleukin-6 (IL-6) and its relationship with PTBE in resected meningiomas.

Methods. Thirty-six benign meningiomas obtained in 36 patients were studied retrospectively. Edema volume was assessed on MR images, and an edema index (EI) was calculated. Interleukin-6 mRNA and protein expression were examined by real-time reverse transcriptase polymerase chain reaction and immunohistochemical staining.

Results. Peritumoral brain edema was found in 16 patients (44%). Neither age, sex, histological subtype, nor tumor location were related to PTBE. The level of IL-6 mRNA was 7.72 times greater in the edema group (EI > 0.2) than in the nonedema group (EI < 0.2; p = 0.011). On immunohistochemical analysis, IL-6 protein was found localized in the cytoplasm of the tumor cells, and was detected in 12 (75%) of 16 cases of edematous meningiomas, but in only 6 (30%) of 20 nonedematous cases. There was a significant correlation between the severity of PTBE and IL-6 expression (p = 0.004).

Conclusions. The authors’ results in this study indicate that IL-6 expression may contribute to the development of brain edema associated with meningiomas. (DOI: 10.3171/2009.4.JNS09158)

KEY WORDS • interleukin-6 • meningioma • peritumoral brain edema

MENINGIOMAS are common primary intracranial tumors, and the mainstay of treatment for these lesions is resection. To improve surgical outcomes, however, neurosurgeons must consider not only how much of the tumor to resect, but also various other factors including location, size, and neural and vascular involvement, which may affect neurological deterioration postoperatively. In particular, PTBE associated with meningioma can cause neurological dysfunction perioperatively and increase injury to neural structures intraoperatively in patients with extensive brain edema.46,58 Various factors have been discussed to clarify their association with PTBE, including age, sex, tumor size, location, and histological differentiation, but the results have been inconsistent.2,4,17,36,54 To date several molecules, including VEGF1,32,45,58 MMP9,46 HIF-1α,32 and tenascin33 have been implicated in the development of PTBE in patients with meningiomas. Cortical penetration of the tumor may also induce PTBE because it demonstrates the disruption of the tumor-brain barrier, and adds the possibility of introducing substances that produce edema into the brain parenchyma.29,54,55 However, the precise pathophysiological mechanism associated with PTBE in meningiomas remains unclear.

Interleukin-6 is a multifunctional cytokine with potent stimulatory effects on immune response in addition to many other functions, including regulation of acute-phase protein synthesis, hematopoiesis, and bone metabolism.27,34,35 Interleukin-6 is expressed in various tumors, including brain tumors.5,11,56 Recently it has been noted that IL-6 induces endothelial barrier dysfunction by in-
creasing endothelial permeability. In addition, IL-6 is associated with edema formation in some organs. These findings suggest that IL-6 could be a crucial factor in edema formation. In the present study we hypothesized that IL-6 plays a role in the development of PTBE in meningiomas. To determine the relationship between PTBE and IL-6, we investigated IL-6 expression in resected benign meningiomas with various levels of PTBE.

Methods

Patients and Tumor Samples

We analyzed tumors in 36 patients who underwent surgery for intracranial meningiomas, diagnosed as Grade I according to the WHO classification, at the Department of Neurosurgery of Korea University Anam Hospital between 2003 and 2007. Before the meningioma was removed, we obtained the patients’ informed consent for the study. There were 8 male and 28 female patients (mean age 53 years, range 17–81 years). All tumor samples were fixed with formalin and embedded in paraffin. Some parts of each sample were stored at −70°C in liquid nitrogen. The histological subtypes were defined according to the WHO classification. Data collected included patient sex and age, and tumor size, location, and histological subtype.

Evaluation of PTBE

All tumor volumes and PTBE were assessed on MR imaging studies in a manner similar to that used in a previous study. The maximum perpendicular diameters (radii a and b) of the tumor were measured on axial images, and the extent in the coronal direction (radius c) was assessed on coronal or sagittal images. The resulting volume of the tumor (Vt) was then calculated using the formula for the volume of a spheroid: Vt = 4π/3 × abc. The total volume (Vt) of the tumor and PTBE were measured on T2-weighted images using the same method. Peritumoral edema volume (Ve) was then calculated as follows: Ve = V – Vt (Fig. 1). The ratio of Ve to Vt was defined as the EI, with zero corresponding to no presence of edema, moderate (0.2 < EI < 1.0), and severe (EI > 1.0; Fig. 2).

Real-Time Reverse Transcriptase PCR

Total RNA was extracted from the tumor tissue using the Trizol reagent (Invitrogen). Approximately 1 µg of a purified RNA sample was used for cDNA synthesis with random primers. The cDNA was prepared with the Super Script kit (Invitrogen) following the manufacturer’s instructions. Reverse-transcribed cDNA was amplified in a final volume of 20 µl using q SYBR Green Supermix (Bio-Rad). The primer sequences were as follows: IL-6 forward 5'-GATGAGGTACAAAGGTCCTGATCCA-3', reverse 5'-CTTCAGCCCTGGGTCCTG-3'; human GAPDH forward 5'-TTACCACCATGGGAAGGC-3', reverse 5'-GGCATGGACCTGGGTCA-3'. The PCR was performed as follows: initial denaturation at 95°C for 5 minutes, followed by 40 cycles at 95°C for 15 seconds, 56°C for 20 seconds, and 72°C for 20 seconds. The resulting relative increase in reporter fluorescent dye emission was monitored in real time with a sequence detector (iCycler iQ Multicolor real-time PCR detection system; Bio-Rad). The fluorescent dye emission was a function of the cycle number and was determined using the sequence detector software (Bio-Rad), resulting in the threshold cycle number at which PCR amplification reached a significant threshold. The value of the threshold cycle number was linearly correlated with the logarithmic value of the quantity of genomic DNA. The expression of IL-6 mRNA was normalized to the RNA loading for each sample by using GAPDH as an internal control.

Immunohistochemical Staining and Assessment of IL-6 Immunoreactivity

Paraffin sections were deparaffinized, microwaved, and blocked serially with 3% H2O2 and 10% normal fetal bovine serum. The sections were then incubated at 4°C overnight with mouse monoclonal anti–IL-6 (1:40 dilution; R&D Systems, Inc.). Diaminobenzidine was used for color precipitation, and the slides were counterstained with hematoxylin to facilitate visualization of the cytoplasm of the immunostained product. Evaluation of the immunostaining was performed by 2 independent observers. The degree of IL-6 staining of the meningioma specimens was evaluated using a 3-tiered system, according to the percentage of positive cells and staining intensity: Grade 0, no expression; Grade 1, moderate expression; and Grade 2, marked expression. The negative controls consisted of phosphate-buffered saline instead of IL-6 antibody. When considering a Grade 2 score for a specimen, we compared the specimen to a control stain in a specified reference tissue (a metastatic tissue specimen from pancreatic cancer for IL-6). The scoring of the staining intensity was conducted in a blind manner to prevent potential bias from knowledge of the clinical data.

Statistical Analysis

We examined the relationship between various fac-
tors and brain edema by univariate and multivariate analyses. All calculations were performed using commercially available statistical software (SPSS version 11.0; SPSS, Inc.). Univariate analysis was performed using the Student t-test, Fisher exact test, chi-square test, Kruskal-Wallis test, Mann-Whitney U-test, Cochran-Mantel-Haenszel test, and Pearson correlation coefficient. The logistic regression method was used for multivariate analyses. Values are expressed as means ± standard errors, and probability values < 0.05 were considered statistically significant.

Results
Clinical Characteristics and PTBE

Data on the clinical characteristics of the patients, EIs, edema grades, and results of the experiments are presented in Table 1. Overall, half of the lesions were meningothelial types, and the majority were located in the convexity, the parasagittal area, or the frontal base. The range of tumor volumes was 1.14–119.00 cm³, with a mean volume of 33.43 ± 28.67 cm³. Apparent PTBE was noted on MR images in 16 (44%) of 36 patients. The results of statistical analysis of the factors influencing the development of PTBE are summarized in Table 2. None of the variables, including age, sex, histological subtype, tumor volume, or location were related to the presence of PTBE on univariate analyses. There was no correlation between age and EI (Pearson correlation coefficient r = -0.116, p = 0.501) or with incidence of edema. Patients younger than 55 years of age had larger tumors than patients older than 55 (43.56 ± 32.74 cm³ vs 24.36 ± 21.50 cm³; p = 0.043), but the EI was not different between the groups (0.85 ± 1.12 vs 0.46 ± 0.64; p = 0.205). Although the meningothelial and transitional lesion subtypes tended to have higher EIs than other subtypes, overall histological subtypes were not significantly associated with the degree of PTBE (p = 0.130). Tumor volume was positively related to the presence of PTBE on multivariate analysis (p = 0.034), but did not also correlate with EI (r = 0.153, p = 0.374). With regard to tumor location, frontal base, falx, and sphenoid meningiomas tended to exhibit severe edema, but this finding did not reach statistical significance (p = 0.134).

Interleukin-6 mRNA Expression Levels in Benign Meningiomas

Interleukin-6 mRNA expression was evaluated in 13 meningioma specimens, including 4 samples from the edema group (EI > 0.2) and 9 samples from the nonedema group (EI < 0.2). The range of IL-6 expression was 0.19–73.52, with a mean of 16.42 ± 23.49. For tumors in the edema group, mean IL-6 expression was 41.33 ± 28.63, whereas in the nonedema group, mean expression was 5.35 ± 8.48 (p = 0.011; Fig. 3).

Interleukin-6 Protein Expression and PTBE

To determine the relationship between IL-6 expression and PTBE, we performed immunohistochemical staining in 36 human meningioma specimens. Interleukin-6 staining in the tumor cells was mostly observed in the cytoplasm (Fig. 4). Twelve (75%) of 16 tumors in the edema group (EI > 0.2) exhibited IL-6 protein expression, whereas the nonedema group showed IL-6 protein expression in only 6 (30%) of 20 cases. The incidence of IL-6 protein expression was significantly higher in the edema than in the nonedema group (p = 0.018; Tables 2 and 3).

We analyzed the correlation between IL-6 expression and the severity of PTBE by subdividing the samples according to EI and IL-6 expression level. As shown in Fig. 5, 14 (78%) of 18 specimens with no IL-6 expression had either no edema or only a minimal amount of edema (EI < 0.2), 3 had moderate edema (0.2 < EI < 1.0), and only 1 had severe PTBE (EI > 1.0). Among the 8 cases with moderate expression, 3 had no or only minimal amounts of edema, 3 had moderate edema, and 2 had severe PTBE. In contrast, 5 (50%) of 10 tumors with marked IL-6 expression showed severe PTBE. There was a significant correlation between edema grade and IL-6 expression (p = 0.004).

Discussion

Approximately 60% of meningiomas are accompanied by PTBE, which may cause perioperative neurological deficits. Meningiomas develop from arachnoid cap cells of the dura mater and grow primarily into extracerebral spaces, unlike gliomas and metastatic cerebral tumors which...
are intraparenchymal lesions that induce vasogenic edema. Therefore, the presence of PTBE in meningiomas was not clear until electron microscopy studies demonstrated similarities between the ultrastructure of the region of PTBE in meningiomas and experimentally induced vasogenic edema.\textsuperscript{22} Meningioma-associated edema is related to tumor invasion into the brain parenchyma,\textsuperscript{23,24,29,41} suggesting that a disruption of the arachnoid barrier followed by impairment of the BBB in the peritumoral tissue is an essential step in the development of PTBE in meningiomas.

There has been controversy regarding the association between PTBE and several factors in meningiomas, in

### TABLE 1: Summary of clinical characteristics in 36 patients with benign meningiomas

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age (yrs), Sex</th>
<th>Location</th>
<th>Pathological Type</th>
<th>Tumor Volume (cm(^3))</th>
<th>EI</th>
<th>IL-6 Grade*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47, F</td>
<td>parasagittal</td>
<td>meningothelial</td>
<td>16.06</td>
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<td>0</td>
</tr>
<tr>
<td>2</td>
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<td>convexity</td>
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<td>0</td>
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<tr>
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<td>fibroblastic</td>
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<td>0</td>
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<td>0</td>
</tr>
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<td>0</td>
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<tr>
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<td>1</td>
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<td>transitional</td>
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<td>0</td>
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<td>12</td>
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<td>meningothelial</td>
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<td>0.19</td>
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<tr>
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<td>0</td>
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<tr>
<td>22</td>
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<td>meningothelial</td>
<td>7.63</td>
<td>0.44</td>
<td>1</td>
</tr>
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<td>23</td>
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<td>0.51</td>
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<tr>
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<td>frontal base</td>
<td>meningothelial</td>
<td>27.69</td>
<td>1.63</td>
<td>2</td>
</tr>
<tr>
<td>32</td>
<td>69, M</td>
<td>frontal base</td>
<td>meningothelial</td>
<td>27.69</td>
<td>1.66</td>
<td>2</td>
</tr>
<tr>
<td>33</td>
<td>38, M</td>
<td>frontal base</td>
<td>meningothelial</td>
<td>119.00</td>
<td>1.72</td>
<td>2</td>
</tr>
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<td>34</td>
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<td>frontal base</td>
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<td>1.77</td>
<td>0</td>
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<td>meningothelial</td>
<td>8.33</td>
<td>4.47</td>
<td>2</td>
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</table>

* The IL-6 grades were assigned as follows: Grade 0, no expression; Grade 1, moderate expression; and Grade 2, marked expression on immunohistochemical staining. CPA = cerebellopontine angle.
Interleukin-6 and meningioma-associated edema

including histological subtypes, tumor volume, and patient age.\textsuperscript{16,22,24,30,36-38,46,55} Regarding histological subtype, certain subtypes of meningiomas have been found to cause severe peritumoral edema.\textsuperscript{24,30,55} In the present study, however, we found that PTBE had no significant correlation with histological subtypes. Although our study did not include the microcystic or secretory subtypes known to cause profound edema,\textsuperscript{9,47,55} the authors of a number of other studies also found no significant correlation between the incidence or degree of PTBE and histological subtype of meningioma, in agreement with our results.\textsuperscript{22,37,38,46} Thus, it is still not proven that the different histological characteristics of the tumor affect the amount of PTBE. Tumor volume may also be an important factor in PTBE in patients with meningiomas. Several authors have indicated that patients with large meningiomas have more severe PTBE than patients with smaller tumors, and have suggested that the degree of tumor compression on the normal brain parenchyma is an important factor causing PTBE.\textsuperscript{22,24,38} According to this assumption, PTBE should be mild in patients with small meningiomas, as well as in older patients who usually have some degree of brain atrophy. However, we did not find EI to be significantly correlated with the tumor volume or age in our patients, and similar results have been reported in other studies.\textsuperscript{30,36,38,46} Therefore, these tumors’ compressive effect may not play a critical role in the development of PTBE.

Recently, several factors have been studied in meningiomas as causal agents of PTBE, including VEGF, MMP-

### Table 2: Summary of univariate and multivariate analyses*

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Univariate</th>
<th>Multivariate</th>
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<tr>
<td>age</td>
<td>0.657</td>
<td>0.526</td>
</tr>
<tr>
<td>sex</td>
<td>0.709</td>
<td>0.060</td>
</tr>
<tr>
<td>histological subtype</td>
<td>0.449</td>
<td>0.442</td>
</tr>
<tr>
<td>tumor volume</td>
<td>0.152</td>
<td>0.034†</td>
</tr>
<tr>
<td>tumor location</td>
<td>0.213</td>
<td>0.794</td>
</tr>
<tr>
<td>IL-6 protein expression</td>
<td>0.018†</td>
<td>0.018†</td>
</tr>
</tbody>
</table>

* The Student t-test, Fisher exact test, and chi-square test were used for univariate analysis, and the logistic regression method was used for multivariate analysis.
† Statistically significant, p < 0.05.

### Table 3: Expression of IL-6 on immunohistochemical staining and brain edema

<table>
<thead>
<tr>
<th>IL-6 Expression Level</th>
<th>No or Minimal Edema (EI &lt; 0.2)</th>
<th>Moderate to Severe Edema (EI &gt; 0.2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none</td>
<td>14</td>
<td>4</td>
</tr>
<tr>
<td>moderate-to-marked</td>
<td>6</td>
<td>12</td>
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</table>

\* The Student t-test, Fisher exact test, and chi-square test were used for univariate analysis, and the logistic regression method was used for multivariate analysis.
† Statistically significant, p < 0.05.
the intensity of IL-6 expression. There was a significant association between the IL-6 expression grade and peritumoral edema (p = 0.004, Cochran-Mantel-Haenszel test).

9, HIF-1α, and tenascin. However, targeted therapies have had limited effect on vasogenic edema.

To determine the edema-associated factors of benign meningiomas, we first examined the microarray analysis as a preliminary study. We divided benign meningiomas into 2 groups based on the presence of PTBE. From the set of differentially expressed genes showing probability values < 0.01 for the paired t-test, and ≥ 4-fold change in the mean expression level, we selected a candidate gene, IL-6, which showed a significant increase in IL-6 upregulation in edema-producing meningiomas (data not shown). To confirm the effect of IL-6 on PTBE, we investigated the correlation between IL-6 expression and PTBE in benign meningiomas.

Interleukin-6 was originally identified as a B-cell differentiating factor and is involved in various activities in different tissues, such as inflammation mediation, including induction of the acute phase reaction, immune response, and cellular differentiation. In the CNS, IL-6 may play a role in the pathogenesis of various diseases. Increased cerebral expression of IL-6 has been demonstrated in neuropathological conditions such as HIV encephalopathy, brain trauma, multiple sclerosis, Alzheimer disease, and CNS infections. In addition, overexpression of IL-6 has been detected in different brain tumors including glioblastoma multiforme, pituitary adenomas, and meningiomas. Interleukin-6 promotes autocrine growth in glioblastomas, and appears to be associated with the development of pituitary adenomas. In meningiomas the action of IL-6 may be contradictory. Some researchers have reported that IL-6 stimulates growth in 60% of meningiomas, whereas others have reported that IL-6 acted to inhibit tumor cell proliferation.

Interleukin-6 may contribute to edema formation under several conditions. It has been reported that peripheral edema after major trauma, sepsis, or surgical procedures increases the level of IL-6 in the body, resulting in fluid shifts between the intra- and extravascular spaces. In particular organs, IL-6 is associated with local edema formation and its expression has been found to induce inflammation and increase capillary permeability, leading to the development or maintenance of pulmonary edema. In addition, vitreous levels of IL-6 were significantly correlated with the severity of macular edema in eye diseases. However, the involvement of IL-6 in edema associated with meningiomas has not been determined. Our results show that IL-6 mRNA expression was ~ 7.72 times higher in the moderate-to-severe edema-producing tumors than in those with no or only minimal amounts of edema. Together with the microarray screening data, this result suggests that increased IL-6 mRNA expression may be associated with PTBE in patients with benign meningiomas, although the sample size was insufficient. We used immunohistochemical analysis, and demonstrated that IL-6 protein expression was statistically correlated with the amount of PTBE in meningiomas. Our results therefore suggest that IL-6 may play a role in PTBE formation in meningiomas. Increased IL-6 expression in meningiomas may be a nonspecific inflammatory reaction to a different stimulus causing edema because IL-6 is a secretory protein produced by various cells, including endothelial cells and macrophages. However, we did not find IL-6 expression in the vascular lumen of meningiomas. In addition, very few inflammatory cells (<1%) are usually identified in meningiomas.

Interleukin-6 influences the integrity of the BBB directly and has been shown to reduce transendothelial electrical resistance and induce changes in the morphological characteristics and permeability of endothelial cells in an in vitro model of the BBB. Systemic administration of IL-6 increases the permeability of the BBB in rats. Moreover, transgenic mice that overexpress IL-6 in astrocytes show extensive extravasation of horseradish peroxidase, indicating an open BBB. In addition, IL-6 can stimulate other substances, including VEGF and MMP-9, which are known to induce PTBE. Therefore, our findings suggest that IL-6 is involved, not only in the dysfunction of the BBB caused by an increase of cerebrovascular permeability, but also through the regulation of other edema-producing molecules indirectly.

Other factors such as pial blood supply and penetration of the arachnoid membrane are also known to be associated with PTBE in patients with meningiomas. Therefore, our findings suggest that IL-6 is involved, not only in the dysfunction of the BBB caused by an increase of cerebrovascular permeability, but also through the regulation of other edema-producing molecules indirectly.

Conclusions

We found that IL-6 is produced in various benign meningiomas and that the severity of PTBE is significantly associated with IL-6 expression. Further studies are needed to determine the precise role of IL-6 in the development of edema in patients with meningiomas.

Disclaimer

The authors do not report any conflict of interest concerning the materials or methods used in this study or the findings specified in this paper.
Interleukin-6 and meningioma-associated edema

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