Platelet-activating factor and edema surrounding meningiomas

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Object. The purpose of this study was to evaluate the involvement of platelet-activating factor (PAF) in the formation of edema surrounding meningiomas.

Methods. Volumes of tumor and peritumoral edema were calculated based on three-dimensional reconstructed magnetic resonance images in 31 patients with intracranial meningiomas. The authors measured tumor concentrations of PAF and localized PAF and leukocytes in the tumors by using immunohistochemical studies. A significant positive correlation was found between peritumoral edema and PAF concentration. Both PAF and leukocyte common antigen were localized to the interstitial tissue of the tumor. Edema production was related to the degree of leukocyte infiltration in meningiomas.

Conclusions. It appears that PAF, which may arise from infiltrating leukocytes, is important to the development of peritumoral edema in patients with meningioma.

KEY WORDS • magnetic resonance imaging • meningioma • peritumoral brain edema • platelet-activating factor • three-dimensional reconstruction

Meningiomas are associated with highly variable degrees of brain edema, which may be severe in small as well as large tumors. Many factors have been implicated in the development of peritumoral edema, including infiltration by leukocytes such as neutrophils, lymphocytes, and macrophages. Leukocytes secrete arachidonic acid metabolites such as prostaglandins and leukotrienes, which may be important in peritumoral edema formation in the brain. Platelet-activating factor (PAF), a potent inflammatory mediator with a wide spectrum of activity and close metabolic links to the eicosanoids, is produced by a variety of cells, including inflammatory cells such as leukocytes. This factor is a chemoattractant for inflammatory cells and an enhancer of vascular permeability. Treatment with a PAF antagonist results in reduction of edema formation after cerebral infarction and neurological trauma. Therefore, PAF is a candidate factor in the causation of edema surrounding meningiomas. To investigate the role of this factor in such cases, we correlated PAF concentrations with volume of peritumoral edema and localized PAF to leukocytes in meningiomas.

Materials and Methods

Patient Population and Tumor Samples

Our study group consisted of 31 patients with meningioma (nine men and 22 women aged 40 to 87 years; mean 64.3 years). The patients were admitted consecutively between May 1989 and July 1994 to the neurosurgical services at Toyama Medical and Pharmaceutical University, Toyama Red Cross Hospital, and Saito Memorial Hospital. We excluded patients with recurrent meningiomas because previous surgery might have disturbed the original anatomical relationships, and patients with cerebral infarction were also excluded, which might have led to overestimation of peritumoral edema.

Tumor Size and Peritumoral Brain Edema

Magnetic resonance (MR) imaging was performed in all patients by using a whole-body 1.5-tesla MR imaging system. Gadolinium-enhanced spin-echo T₁ (TR 510 msec, TE 15 msec) and T₂ (TR 2500 msec, TE 90 msec) weighted images were obtained in two sets of planes (horizontal and sagittal, horizontal and coronal, or coronal and sagittal) through the tumor and surrounding edema. The volumes of the tumor and tumor plus edematous tissue were calculated from the three-dimensional reconstructed gadolinium-enhanced T₁- and T₂-weighted images. The computer system consisted of a graphics workstation and an image scanner. After the original cross-sectional images were scanned, they were interpolated to obtain an image volume measured in cubic voxels. At the graphics workstation, the data were subjected to image processing and volume rendering manipulations to produce three-dimensional views of the region of interest. Tumor was distinguished from edematous tissue semiautomatically, based on the minimum and maximum gray values in the 8-bit image. The volume of peritumoral edema was obtained by subtracting the volume of the tumor from that of the tumor and surrounding edematous tissue. An edema index (EI) was calculated by dividing the volume of the tumor plus peritumoral edema by that of the tumor, with an EI of 1.0 indicating no peritumoral edema.
Histological and Immunohistochemical Findings

Meningiomas were examined with the aid of a light microscope after routine histological processing including hematoxylin and eosin staining and were classified according to the World Health Organization classification. Tumor tissues frozen at −20°C were cut at a thickness of 5 μm by means of a cryostat, and sections were mounted on glass slides that were then exposed to primary anti-PAF immunoglobulin G (IgG) antibody for PAF staining or to anti-leukocyte common antigen (LCA) for leukocyte staining. Sections were subsequently incubated with biotinylated anti–rabbit IgG. Finally, immunoreaction products were visualized by incubation in a solution of 0.02% 3,3'-diaminobenzidine tetrahydrochloride, 0.3% nickel ammonium sulfate, and 0.005% H2O2 in 0.05 M Tris buffer (pH 7.6).

Concentration of PAF in Tumors

Tumor samples were homogenized in methanol by using a polytron homogenizer (2 g tumor/6 ml methanol). The homogenates were mixed overnight in a magnetic stirrer and centrifuged at 1500 G for 15 minutes. The extracts were stored at −20°C. The PAF concentration was measured according to the method of Yamada, et al. In brief, impurities were removed from the extract by column purification, and the PAF concentration was analyzed by using gas/mass spectrometry.

Statistical Analysis

We used the chi-square test for PAF concentrations, comparing differences in distribution of values below and above the detection limit of the assay. Data are reported as the mean ± standard deviation. Dunnett’s test was used for comparison of EI among meningothelial, angiomatous, and anaplastic meningiomas. Student’s t-test was used for comparisons of EI among tumors with a low (<50%) and high (≥50%) degree of interstitial leukocytic infiltration. The relationship between PAF content and EI was evaluated by using Pearson’s correlation coefficient. The coefficient was analyzed by a t-test. Probability values of less than 0.05 were accepted as statistically significant.

Sources of Supplies and Equipment

The MR imaging system (Magnetom H15) was purchased from Siemens, Erlangen, Germany. The three-dimensional computer graphics system (Advans) was obtained from Tomiki Medical Instrument Co., Kanazawa, Japan, and included a graphics workstation (Indy) from Silicon Graphics, Mountain View, CA, and an image scanner (GT-6500) from Epson, Suwa, Japan.

The rabbit anti-PAF IgG was kindly donated by Dr. K. Karasawa, Teikyo University, Sagamiko, Japan. For immunohistochemical analyses, mouse anti–human LCA monoclonal antibody was obtained from Nichirei Co., Tokyo, Japan. The goat biotinylated anti–rabbit IgGs, rabbit biotinylated anti–mouse IgGs, rabbit IgG, and mouse IgG were purchased from Dakopatts A/S, Glostrup, Denmark.

Results

Peritumoral Edema, PAF, and Histological Type

Histological examination revealed that 21 meningiomas were meningothelial, four were angiomatous, four were anaplastic, and two were fibroblastic. Our method of analysis detected PAF in excess of 50 pg/g of tissue. We used the chi-square test to compare the distribution of PAF concentrations of less and more than 50 pg/g tissue among the four types of meningioma. No statistically significant difference in PAF concentration was detected among these histological subtypes (data not shown). There was also no difference in EI among subtypes of meningioma, except between angiomatous and meningothelial subtypes (15.6 ± 6.63 in four tumors compared with 3.58 ± 2.79 in 21, respectively; p < 0.05 by Dunnett’s test).

Concentration of PAF and Peritumoral Brain Edema

We estimated the correlation between EI and PAF concentration in tumors with more than 50 pg/g tissue. Among 13 meningiomas with PAF contents of more than 50 pg/g, a significant positive correlation was detected between PAF concentration and EI (Y = 0.0377X + 0.294 in 13 tumors, r = 0.839, p < 0.001; Fig. 1). Among me-
ningothelial meningiomas, there also was good correlation between PAF and EI (Y = 0.0376X – 0.0274 in seven tumors, r = 0.974, p < 0.001; Fig. 1).

Immunohistochemical Studies

The PAF was localized to the interstitial tissues of the meningiomas. The localization and distribution of LCA paralleled those of PAF (Fig. 2).

Degree of Leukocyte Infiltration and Peritumoral Brain Edema

Leukocyte infiltration in the tumor was evaluated in a blinded manner in four microscopic fields by using LCA staining. The degree of leukocyte infiltration was classified into four grades: Grade 1 (12.5%), Grade 2 (37.5%), Grade 3 (62.5%), and Grade 4 (87.5%). We calculated the average degree of leukocyte infiltration, dividing the tumors into two groups with more and less than 50% leukocyte infiltration. The EI of tumors with more than 50% leukocyte infiltration was higher than in those with less (7.6 ± 6.53 in 17 tumors compared with 1.88 ± 0.529 in 13 tumors, respectively; p < 0.01, Student’s t-test, Fig. 3).

Discussion

Peritumoral edema is an important complication of intracranial meningioma. Despite extensive clinical and experimental investigation, the pathogenesis of peritumoral edema remains unclear. Various approaches used to estimate brain edema have included qualitative grading on computerized tomography scans, as well as quantitative methods such as multiplying the largest area of edema by the number of computerized tomography slices showing edema or multiplying the three longest axes; neither method yields accurate volumes. Go, et al., recently reported a method that provides a fairly accurate measurement of edema volume by integrating the cross-sectional area of edema on serial MR slices. We adapted this approach to three-dimensional computer reconstruction, which enables us to measure the volume of peritumoral edema.

Vasogenic and cytotoxic edema, disruption of the blood-brain barrier, and impaired microcirculation occur after cerebral ischemia and head trauma, and ultimately contribute to secondary loss of neuronal tissue. The PAF antagonists reduce edema formation and diminish the area of increased blood-brain barrier permeability in the brain after ischemia and trauma. Therefore, PAF may be involved in the pathogenesis of edema formation. The PAF is produced by a variety of cells such as neutrophils, platelets, monocytes, macrophages, and endothelial cells. Shinonaga, et al., have found an excellent correlation between the degree of macrophage infiltration and the amount of peritumoral edema in meningiomas. These authors have postulated that arachidonic acid metabolites secreted by macrophages interfere with vascular permeability. Platelet-activating factor, a chemical mediator of inflammation with close metabolic links to eicosanoids such as prostaglandins and leukotrienes, is a potent enhancer of vascular permeability. Therefore, PAF may be among the most important contributors to edema formation. In the present study we directly analyzed PAF concentration in meningiomas and correlated these concentrations with the degree of peritumoral edema (Fig. 1). The PAF content in tumors correlated significantly with
Platelet-activating factor and edema in meningiomas

peritumoral edema not only in meningiomas as a group but also in the most common subtype, meningothelial meningioma (Fig. 1). The EI does not correlate with symptoms because total tumor volume and peritumoral edema affect the appearance of symptoms, but tumors with higher EIs may show symptoms earlier. The EI may be determined by many factors, including PAF.

The origin of PAF is an interesting problem. Prostaglandin and thromboxane production has been reported in cells isolated from meningiomas, which were free of platelets and only minimally contaminated by leukocytes. Therefore, the origin of eicosanoids in meningiomas is unclear. Although PAF concentrations in isolated meningioma cells are not known, the PAF in the tumors we studied was located in the interstitial tissue, a location coincident with LCA staining (Fig. 2). Furthermore, the degree of peritumoral edema was correlated with the degree of leukocyte infiltration in the tumors (Fig. 3). Therefore, release of PAF from infiltrating leukocytes appears to be more important than release from tumor cells. Accumulation of PAF may occur through the circle consisting of PAF and leukocyte infiltration.

Tumor location, vascular supply, cerebrocortical destruction, dural sinus involvement, and the histological type of the tumor all have been implicated in the development of brain edema, which most likely is a multifactorial process. Platelet-activating factor arising from leukocytic infiltration may be important among these influences.

References


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