# Meningioma peritumoral edema

More than half of all meningiomas develop peritumoral edema.

In atypical meningiomas bone involvement and large peritumoral edema are associated with increased tumor progression [1].

Peritumoral edema on preoperative CT and MR studies and tumor pial vascularization as seen on selective angiography can be used to predict the surgical plane of cleavage in meningiomas. The association between tumor size and a subpial surgical plane may be explained by a more pial vascularization seen on angiography. Meningiomas with a location in eloquent cortex and a subpial dissection plane should be considered a high-risk group [2].

## Mechanisms

The mechanisms behind its development are not clearly understood. It is believed that due to tumour growth and local tissue hypoxia, angiogenesis is increased and leads to the formation of PTBE.

Peritumoral brain edema in patients with meningiomas may depend on AQP4 expression grades and not on tumor grade, tumor volume, Ki-67 expression, and cell count. The amount of edema predicted AQP4 expressions with moderate-to-good sensitivity and specificity [3].

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The angiogenic protein vascular endothelial growth factor A (VEGF-A) is believed to be involved in the formation of PTBE around meningiomas, as several studies have found that it is increased in meningiomas with PTBE. VEGF-A is also known as vascular permeability factor due to its ability to increase the permeability of capillaries. Paper I examines the VEGF-A protein and mRNA levels in 101 intracranial meningiomas. The PTBE is quantified on MRI, and capillary length and tumour water content are measured and compared to control brain tissue. Possible co-factors to PTBE like meningioma localization and subtypes are also examined. Forty-three of the patients have primary, solitary, supratentorial meningiomas with PTBE. The correlation between PTBE or edema index with the VEGF-A protein and mRNA, capillary length, and tumour water content is investigated in these patients. A novel method is used for mRNA quantification. It involves direct amplification of the mRNA with probes and branched DNA in order to produce a chemiluminescence signal that can be measured using a luminometer. The paper shows that the oedema index is correlated to the VEGF-A protein and mRNA, and that capillary length is correlated to the PTBE. It also finds that VEGF-A protein and mRNA, capillary length and water content is increased in meningiomas compared to control tissue, suggesting that VEGF-A is produced in, and possibly secreted from the meningiomas. In addition, supratentorial meningiomas are shown to have larger PTBE compared to infratentorial meningiomas, suggesting that infratentorial meningiomas are diagnosed and removed earlier, due to earlier symptom development based on the anatomical features of the fossa posterior. Finally, a gender-specific difference in tumour water content and VEGF-A protein is revealed (higher and lower in females, respectively). Paper II is a method-comparison study pitting the chemiluminescence assay against the often used quantitative real-time reverse transcription polymerase chain reaction (RT-qPCR) assay. In RT-qPCR, RNA is isolated, measured, reverse transcribed, purified, amplified via real-time PCR, and analyzed. The method is robust and reliable, albeit laborious to some extent. The chemiluminescence assay detects RNA directly without the need for RNA purification, complement

DNA synthesis or cyclic amplification. By comparing the output of the two protocols to a dilution series ranging from 1 to 128 times of the homogenized samples, the precision of the protocols is measured. Furthermore, VEGF-A/GAPDH ratios are quantified for 15 tissue samples and the results compared between the two protocols, showing significant correlation. The study finds that the chemiluminescence assay is competitive to RT-qPCR, and reflects a similar pattern in gene expression measurement with a similar precision. Whether one method or the other should be used depends on the variability of the samples, budget, and time. RT-qPCR has a much wider dynamic range, and is preferable in case of significant sample inter-variability. It is also less expensive, and gives the user more flexibility as homemade reagents can be used. On the other hand, the chemiluminescence assay is straight forward, requires less hands-on-time, and can be used on formalin-fixed and paraffin-embedded (FFPE) tissue. Paper III continues the investigations in paper I. The sample size is increased so that 22 angiomatous and secretory meningiomas are compared to 40 non-angiomatous meningiomas and 10 control brain tissue samples. Angiomatous and secretory meningiomas are chosen because they are known to have larger PTBE compared to other meningiomas. In addition to VEGF-A, capillary length, and PTBE, the VEGF-A tyrosine kinase receptor VEGFR-2 mRNA and protein levels are also examined. VEGFR-2 is a transmembrane receptor found on endothelial cells. It binds VEGF-A and thereby increases angiogenesis. VEGFR-2's co-receptor neuropilin-1 is also examined. Neuropilin-1 is an agonist of angiogenesis through complex-binding of VEGF-A, but it can also work as an inhibitor through competitive binding of semaphorin-3A. The complex binding of semaphorin-3A to neuropilin-1 can also induce endothelial cell apoptosis, thus working as an antagonist of angiogenesis. The study finds that VEGF-A mRNA, VEGF-A protein, and neuropilin-1 mRNA are higher in angiomatous and non-angiomatous meningiomas compared to controls. VEGFR-2 protein is higher, and neuropilin-1 protein lower in angiomatous meningiomas compared to controls. The mean capillary length is 3614 mm/mm3 in angiomatous, 605 mm/mm3 in non-angiomatous meningiomas, and 229 mm/mm3 in the controls. Non-angiomatous and angiomatous meningioma patients have equally sized tumours. The mean PTBE around the angiomatous meningiomas is 695 cm3, i.e. 477 cm3 larger than the non-angiomatous meningiomas ($p = 0.0045$), and the mean oedema index is twice the size compared to the non-angiomatous meningiomas. Further comparison between the two meningioma groups shows that mean VEGF-A mRNA, VEGFR-2 protein, and neuropilin-1 mRNA is significantly higher and neuropilin-1 protein is lower in the angiomatous meningiomas. We believe that the VEGF-A pathway participates in the formation of PTBE in meningiomas by inducing formation of “leaky” capillaries, resulting in secretion of VEGF-A and plasma to the peritumoural brain tissue. It may therefore be worth pursuing therapies targeted directly against VEGF-A and its receptors through drugs like bevacizumab, sorafenib, sunitifib, and cediranib [4)].

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