

Diffusion weighted imaging in the normal appearing white matter of glioma patients

PhD Thesis

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1. Introduction

Central nervous system (CNS) neoplasms affect adults and children of all ages, and they are the second leading-cause of tumor-related death in children and adolescents. CNS tumors are classified as primary tumors, if they arise from brain tissue cells, or metastatic tumors, if they originate from cancers outside of the CNS. Glial cell-derived tumors account for 27% of all primary CNS tumors, and 80% of malignant CNS neoplasms. The annual incidence is 18 054 /100 000 individuals and they occur at a rate of 5.55/100 000 individuals annually in the United States according to the Central Brain Tumor Registry of the United States. They require special attention in the field of neuro-oncology due to their complex behavior and histopathology and relatively high mortality rate.

Despite the improvements of diagnostic methods and surgical techniques and the intense effort in developing new, targeted therapies the prognosis for patients with glioma still remains poor. Only 5.1% of patients with the most malignant glioma subtype survive 5 years after diagnosis. A possible reason for the poor prognosis is the diffuse, infiltrative nature of gliomas which hinders complete resection and reduces the efficacy of local radiation therapy or radiosurgery.

Tumor infiltration in macroscopically inconspicuous areas distant from the tumor was shown in post mortem human brains. Recently, several research groups tried to show tumor infiltration with magnetic resonance imaging (MRI). Abnormalities were revealed in the contralateral normal appearing white matter (NAWM) of glioma patients with diffusion tensor imaging and whole brain spectroscopy,

and they explained their findings with the presence of tumor infiltration. However, the question may arise, whether these diffusion alterations are really related to infiltrative tumor cells, and whether apparent diffusion coefficient (ADC) can be used as a marker of tumor infiltration.

Water diffusion in the brain is affected by tissue microstructure, and thus it can be used to monitor changes accompanying various pathologies. Signal decay with high b factors can better be described with a biexponential function. This model assumes a fast and slow diffusion pool with fast and slow diffusion coefficients, whose origin is yet unclear. The most reasonable explanation is that the slow diffusion pool corresponds to highly structured water layers bound to membrane surfaces and cytoskeleton (i.e. hydration shell around proteins and macromolecules) and the fast diffusion pool originates from the remaining extra and intracellular tissue water. Consequently, diffusion imaging with an extended b factor range enables more specific tissue characterization and differentiation. More complete understanding of diseases could promote the development of more efficient therapies which might result in improved outcome.

2. Objectives

The primary aim of this thesis was to clarify the nature of elevated ADC in the NAWM of glioma patients.

An indirect way to prove or exclude the role of distant tumor infiltration in altering diffusion in the contralateral NAWM is to examine the contralateral NAWM of patients with non-infiltrative tumors. If ADC is elevated in the NAWM of both infiltrative tumor (i.e. glioma) and non-infiltrative tumor (i.e. meningioma) patients, the diffusion alteration

cannot be explained exclusively by the presence of tumor infiltration. Therefore, the primary aim of the first study was to determine if diffusion abnormality was also present in the contralateral NAWM of patients with non-infiltrative tumors such as meningiomas.

The secondary aim was to search for other possible factors that could contribute to ADC elevation in the contralateral NAWM. Since a certain amount of mass effect is present in tumors regardless of their infiltrative or non-infiltrative behavior, the further purpose of the study was to investigate its role in causing contralateral NAWM diffusion abnormalities.

The goal of the second study was to further clarify the nature of elevated ADC in NAWM of glioma patients with the more detailed biexponential diffusion analysis and to reveal if the observed diffusion alterations were region specific or global.

3. Methods

Increased diffusion in the normal appearing white matter of brain tumor patients: is this just tumor infiltration?

Twenty-seven patients with histologically verified glioma (13 females, 14 males; mean age: 49.0 ± 16.9 years, grade II-IV), 22 meningioma patients (15 females, 7 males; mean age: 53.5 ± 12.3 years) and two groups of age- and sex-matched healthy controls underwent diffusion weighted imaging (DWI) on a 3T MR before any treatment or intervention. ADC values were calculated in the entire NAWM of the hemisphere contralateral to the tumor. ADC values of the NAWM were compared between groups with Mann-Whitney U-test and multiple linear regression. The relations of ADC in NAWM to glioma grade and to tumor volume were also investigated.

Biexponential diffusion alterations in the normal appearing white matter of glioma patients might indicate the presence of global vasogenic edema

Twenty-four newly diagnosed glioma patients (10 females, 14 males, mean age: 42.29 ± 11.44 years, grade II-IV) and 24 matched control subjects underwent diffusion weighted imaging at 3T. Diffusion parameters were calculated using monoexponential and biexponential models. ADC values were measured in the entire NAWM of the hemisphere contralateral and ipsilateral to the tumor. In the contralateral NAWM, regional ADC values were assessed in the frontal, parietal, occipital and temporal NAWM. Both total hemispheric and regional diffusion values were compared between patient and control groups by Student's t test or two tailed Mann-Whitney-U test according to the statistical distribution of the data. Two-way mixed ANOVA was performed to evaluate whether regional differences in diffusion parameters were significant between patients and controls.

4. Results

Increased diffusion in the normal appearing white matter of brain tumor patients: is this just tumor infiltration?

ADC values of the contralateral NAWM were significantly higher in both glioma and meningioma patients compared to controls ($P=0.0006$ and $P=0.0099$, respectively, Fig. 1a). ADC value was higher in the NAWM of high grade gliomas than in low grade gliomas ($P=0.0181$) and in healthy control subjects ($P=0.0003$)(Fig. 1b). ADC did not depend on tumor volume in any of the patient groups.

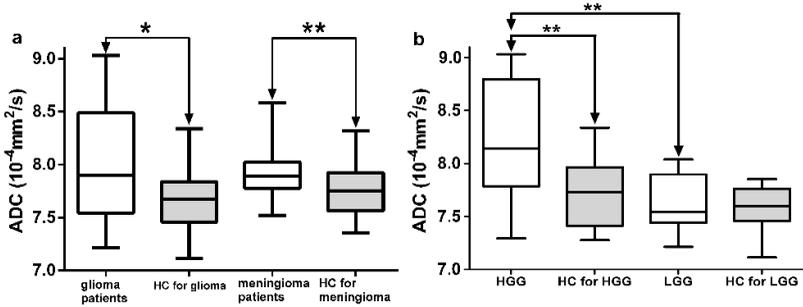


Fig. 1. a) Boxplot illustrating the significantly increased ADC in the contralateral NAWM of glioma and meningioma patients compared with healthy control subjects. b) Boxplot illustrating the significantly increased ADC in the contralateral NAWM of HGG patients compared with healthy control subjects and LGG patients. Whiskers are set at minimum and maximum, the horizontal line marks the median, whereas box indicates the interquartile range (25-75%). * indicates $P < 0.05$, ** indicates $P < 0.01$. HC: healthy control, HGG and LGG: high and low grade glioma.

Biexponential diffusion alterations in the normal appearing white matter of glioma patients might indicate the presence of global vasogenic edema

Results of the hemispheric and regional analyses are presented on Fig 2. ADC_{mono} and ADC_{fast} were significantly higher than control values in all investigated regions except the temporal NAWM ($P < 0.04$). ADC_{slow} was significantly increased in the total contralateral, the frontal and parietal NAWM ($P < 0.03$), while p_{slow} was decreased in both total hemispheric NAWM and the parietal NAWM of glioma patients compared to controls ($P < 0.04$). Significant differences were observed in all diffusion parameters among the NAWM of the four lobes of the contralateral hemisphere in both groups ($P < 0.0001$), these regional differences were similar in patients and controls ($P > 0.05$). Hemispheric ADC_{mono} and p_{slow} differences were different between groups ($P < 0.05$).

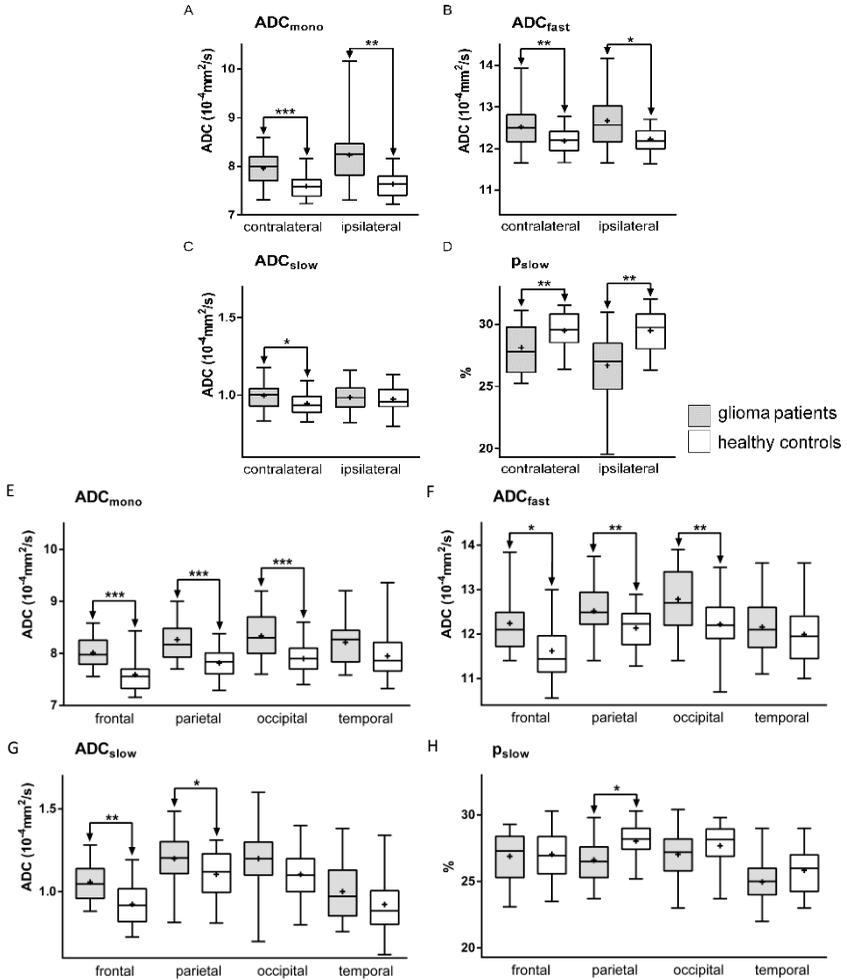


Fig. 2. Results of the hemispheric (A-D) and regional (E-H) analyses. Comparisons of monoexponential ADC_{mono} values (A and E), biexponential ADC_{fast} (B and F), ADC_{slow} (C and G) and p_{slow} (D and H) in the NAWM of glioma patients and healthy controls. In the boxplots, whiskers are set at minimum and maximum, the horizontal line marks the median, + indicates the mean, whereas box indicates the interquartile range (25-75%). * indicates P<0.05, ** indicates P<0.01, *** indicates P<0.001. Contralateral and ipsilateral indicate the total NAWM in the hemisphere contralateral and ipsilateral to the tumor. Frontal, parietal, occipital and temporal indicate the regional NAWM ROIs in the hemisphere contralateral to the tumor.

5. Discussion

Altered diffusion in the NAWM of glioma patients has previously been explained by tumor infiltration. In this thesis we intended to clarify the nature of elevated ADC in the NAWM of glioma patients.

Our study tested the hypothesis whether abnormal ADC values in the normal appearing white matter contralateral to brain tumors can be explained exclusively by tumor infiltration.

An indirect way to test this hypothesis was to check if ADC was altered in the contralateral NAWM of patients with non-infiltrative tumors. We assumed, if ADC was increased in the NAWM of both infiltrative tumor (i.e. glioma) and non-infiltrative tumor (i.e. meningioma) patients, the diffusion alteration could not had been explained exclusively by the presence of tumor infiltration.

Our results revealed elevated ADC in the contralateral NAWM of both infiltrative and non-infiltrative tumor patients that might suggest that the effect of infiltrating tumor cells is not the only reason for the alteration. One alternative explanation, mass effect, was investigated and not found to play a role in increasing ADC values in the contralateral NAWM, since ADC in the contralateral NAWM was not related to tumor volume. The literature was searched for other possible factors that could explain our results (Figure 3). There are complex mechanisms that might be present in both infiltrative and non-infiltrative tumors possible related to the secretory activity of the tumors. Besides these, effects of tumor infiltration in infiltrative tumors might also contribute to elevated ADC. This contribution seems to be greater in the NAWM of high grade glioma patients than in low grade glioma patients.

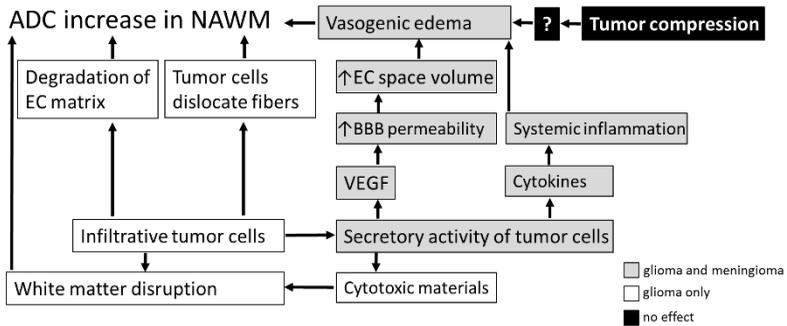


Fig. 3. Summary of possible factors based on literature data that could contribute to ADC elevation in the NAWM. Grey boxes: factors possibly present in both gliomas and meningiomas. White boxes: factors that might only be present in infiltrating tumors such as gliomas. Black boxes: factors whose contribution to increased ADC appears unlikely based on our results. Abbreviations: EC: extracellular, BBB: blood brain barrier. VEGF: vascular endothelial growth factor.

In the second study, we aimed to reveal the cause of observed diffusion abnormality prospectively with the slow (structured) and fast (free) diffusing water compartment model described by LeBihan. The biexponential analysis revealed increased ADC_{mono} , ADC_{fast} and ADC_{slow} values and decreased p_{slow} value in the NAWM of the unaffected hemisphere of glioma patients, which suggested the presence of global vasogenic brain edema in glioma patients. This study revealed that regional differences in patients followed those found in controls, which also supported the global nature of the phenomenon. Besides the presence of edema, tumor infiltration might be responsible for the diffusion abnormalities in the ipsilateral NAWM, however, the increase in ADC is probably not an indicator of tumor infiltration only.

In conclusion, gliomas affect the brain in areas where they are not macroscopically present. Although this thesis intended to clarify the

reason for altered diffusion in NAWM, it is still not clear what happens exactly and whether these diffusion abnormalities are associated with the poor prognosis of gliomas. Our retrospective study including non-infiltrative and infiltrative patients showed, that altered diffusion in the NAWM is not exclusively caused by tumor infiltration, although the difference between low and high grade gliomas might indicate some degree of infiltration. One alternative explanation, mass effect was excluded during the first study. The potential role of vasogenic edema in causing the observed diffusion alterations was shown in the second, prospective study. Our results might contribute to the development of diagnostic or prognostic methods in the future.

6. List of publications

6.1. Articles related to this thesis

Horvath A, Perlaki G, Toth A, Orsi G, Nagy S, Doczi T, Horvath Z, Bogner P (2016) Increased diffusion in the normal appearing white matter of brain tumor patients: is this just tumor infiltration? *Journal of Neuro-Oncology* 127(1):83-90. **IF: 2.754** (in 2015)

Horvath A, Perlaki G, Toth A, Orsi G, Nagy S, Doczi T, Horvath Z, Bogner P (2016) Biexponential diffusion alterations in the normal-appearing white matter of glioma patients might indicate the presence of global vasogenic edema. *Journal of Magnetic Resonance Imaging* 44(3):633-41. **IF: 3.250** (in 2015)

6.2 Articles unrelated to this thesis

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