The mean transit time (MTT) reflects the amount of blood brain barrier breakdown due to microvascular proliferation in glioblastoma demonstrated by perfusion weighted imaging (PWI)

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Abstract

One of the characteristic histopathological findings in glioblastoma is a pathological microvascular proliferation. Using a bolus-traced dynamic T2*-weighted EPI sequence, maps for rCBV, rCBF and MTT can be determined. In glioblastoma rCBV and rCBF were increased compared to the grey matter of the affected hemisphere, whereas grey matter of the affected or non-affected hemisphere did not differ. Furthermore MTT was doubled in the tumor tissue displaying mechanisms of leakage of contrast agent even though the brain tumor receives more volume at a higher flow. This reflects arterio-venous shunting in the glioblastoma with an additional steal effect of the tumor.

Introduction

Highly malignant Glioblastomas are the most frequent brain tumors. In histopathological specimen nuclear atypia, mitosis, necrosis and microvascular proliferation is found (1, 2). Still, the pathomechanism of tumor genesis is unknown. In conventional MR imaging areas of a breakdown of the blood brain barrier with a characteristic enhancement after intravenous contrast agent application are found. Perfusion weighted imaging (PWI) has been used to map hemodynamic changes in both tumor and stroke. In PWI of brain tumors a differentiation between high and low grade gliomas has been reported (3, 4). Correlation between hemodynamic changes demonstrated by MR imaging and possible pathophysiological mechanisms are rarely reported. Using perfusion weighted imaging (PWI) we investigated whether characteristic hemodynamic changes in glioblastoma can be found in maps for relative regional blood flow (rCBF) and volume (rCBV) as well as the mean transit time (MTT) in relation to the unaffected surrounding tissue. We hypothetize, that high malignant brain tumors produce a steal effect from the surrounding tissue to support its increased demand. Furthermore we tried to examine parameters reflecting the amount of blood brain barrier brakedown.

Material and methods

Patients: Perfusion weighted MR imaging (PWI) was performed in 15 patients with glioblastoma after written consent was obtained prior to neurosurgical removal. Three of the patients had recurrent glioblastoma.

MRI: PWI was performed on a 1 Tesla scanner (Siemens, Magnetom Expert, Erlangen Germany) using a standard head coil. A multislice T2*-weighted EPI-sequence (TR / TE = 2000 / 62 ms, FOV 240cm matrix 128x128, slice thickness 6mm, 40 images per slice) was used for hemodynamic mapping. The volume of interest was divided into two blocks, the lower positioned at the level of the medial cerebral artery (MCA) to depict the arterial input function, the upper was placed through the tumor. After an initial baseline period of 8 images per slice a double dose of contrast agent (Ga-DTPA, Schering, Berlin, Germany) was injected at a flow rate of 6ml/sec. Before and after the PWI measurement, a spin-echo T1-weighted images with identical slice positions were acquired.

Data analysis: After determination of the arterial input function from either the MCA or the ICA, maps of relative rCBF, rCBV and MTT were created using a software program (5, 6). The T1-weighted images were analyzed in order to exclude major vessels in the tumor as main source of maximum values in the defined regions of interest from the analysis of rCBF, rCBV and MTT. Mean and maximum values were examined in the tumor as such, the tumor rim as well as the grey and white matter of the affected and non-affected hemisphere.

Results

The highest values for MTT, rCBV and rCBF were found in the tumor. The mean transit time (MTT) of the contrast agent was not different in the affected and non-affected hemisphere. Mean values for MTT in the tumor did not differ from those of the grey matter of the affected hemisphere. There was a close correlation between maximum values of MTT in the tumor and the adjacent grey matter (R=0.59). Furthermore, values of the grey matter of the affected hemisphere were halved in relation to maximum values in the tumor ($p<0,0001$).

Values for rCBV and rCBF in the grey matter did not differ significantly between the affected and the non-affected hemisphere (paired t-test). A highly significant correlation was found in rCBV between the affected ($rCBV_i$) and non-affected ($rCBV_c$) hemisphere ($R^2=0,94$; $p<0,0001$). For rCBF, a highly significant correlation also was found between affected and non-affected hemisphere ($R^2=0,97$; $p<0,001$) with rather elevated values in the affected hemisphere. Maximum values of rCBV and rCBF in the tumor ($rCBV_t$ and $rCBF_t$) were found in the tumor margin of all patients. No difference was found between glioblastoma or recurrent tumors. Both $rCBV_t$ and $rCBF_t$ were significantly increased compared to the adjacent grey matter ($p<0.001$) with a highly significant correlation between $rCBV_i$ and $rCBV_t$ in favor of $rCBV_t$ ($R^2=0,64$; $p<0,0005$) and between $rCBF_i$ and $rCBF_t$ ($R^2=0,58$; $p<0,001$) in favor of the tumor respectively.

Conclusion

After excluding elevated values in the tumor caused by the neoangiogenetic vessels, there still remained maximum values in the tumor tissue that demonstrated significant hemodynamic characteristics of the tumor compared to the grey matter of the affected hemisphere, which did not differ from the grey matter of the non-affected hemisphere as demonstrated by statistical analysis (paired t-test).

MTT was halved in the grey matter of the affected hemisphere in relation to the tumor. The relative rCBF was elevated in the tumor, respectively. Furthermore relative rCBV in the tumor was above a level reached by the grey matter of the affected-hemisphere, that again did not significantly differ for the values of the non-affected hemisphere. Due to its increased demands, glioblastoma “steal” blood from the surrounding brain tissue with elevated rCBV that passes the tisue at a higher flow (rCBF). However, the mean transit time was doubled compared to the adjacent brain parenchyma demonstrating that contrast agent remains in the tissue due to leakage through the missing blood brain barrier in the neoangiogenetic vessels in the tumor leading to the specific contrast enhancement found on T1 weighted images. As a tendency rCBF was slightly elevated in the affected hemisphere which seems to compensate this AV-shunting at a baseline rest condition.

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