Extent of Vascular Dysregulation in Diffuse Gliomas is Determined by IDH1 Mutation Status

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Introduction

Mutation of the isocitrate dehydrogenase 1 (IDH1) gene is an important prognostic marker in diffuse gliomas. IDH1 wild-type tumors have worse clinical outcomes and more invasive imaging features than their IDH1 mutant counterparts. However, the degree of glioma infiltration outside radiologically-defined tumor borders has not been quantified. Blood oxygenation level dependent (BOLD) fMRI can detect glioma-induced disruption of normal vascular regulatory function that occurs beyond conventional tumor margins. The present study quantifies the spatial extent of vascular dysregulation associated with IDH1 mutation status in patients with treatment-naïve diffuse gliomas. We hypothesized that IDH1 wild-type gliomas will have larger areas of BOLD signal abnormality in the surrounding brain tissue and will ultimately demonstrate greater residual disease following surgical resection of the tumor.

Methods

BOLD maps of vascular dysregulation were generated from preoperative fMRI scans of 34 treatment-naïve patients with WHO grades II-IV gliomas. IDH1 mutation status was determined by immunohistochemical staining for the mutant IDH1 R132H protein. We directly compared the spatial overlap of vascular dysregulation measured by BOLD fMRI and the radiologically-defined tumor using the Dice coefficient. We also performed a regression analysis to compare the relationship between percent of tumor resected and fraction of residual BOLD abnormality.

Results

The BOLD abnormality extended further beyond the tumor margins in IDH1 wild-type gliomas than in IDH1 mutants (p=2x10^-8)(Fig. 1). Furthermore, after controlling for patient age, histological subtype, WHO grade, and 1p/19q co-deletion status, IDH1 mutation status remained a significant predictor of the extent of vascular dysregulation beyond the tumor margins (p=0.0001). Finally, surgical resection eliminated a smaller fraction of the BOLD abnormality in IDH1 wild-type tumors (p=0.0016)(Fig. 2).

Figure 1

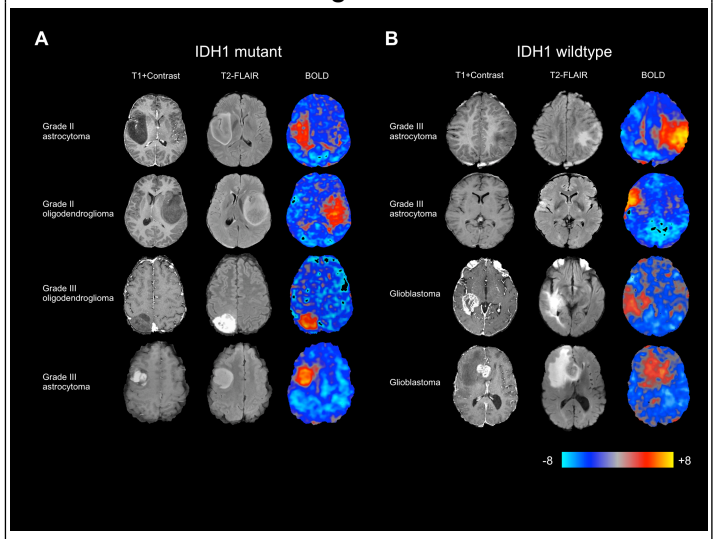

Figure 1 - Preoperative maps of vascular dysregulation for IDH1 mutant and wild-type groups. (A) In the four IDH1 mutant gliomas, the BOLD abnormality is mostly confined to the T2-FLAIR hyperintensity (mean Dice coefficient = 0.666). (B) The four IDH1 wild-type gliomas demonstrate regions of vascular dysregulation beyond the tumor borders defined by structural imaging (mean Dice coefficient = 0.333).

Figure 2

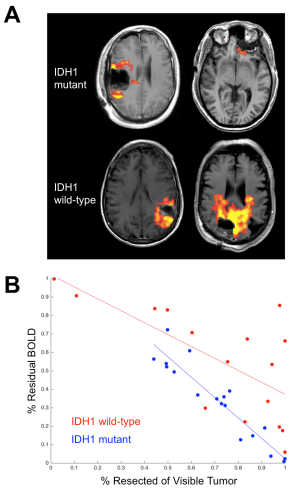

Figure 2 – Post-operative residual BOLD analysis. (A) Four examples of residual BOLD abnormality following resection. IDH1 mutants show smaller residual volumes than wild-type tumors. (B) Linear regression of the fraction of residual BOLD abnormality as a function of fraction of visible tumor resected. These data show larger residual BOLD abnormality in wild-type tumors even after total resection of visible tumor.

Conclusions

IDH1 mutation status is a critical variable affecting extent of infiltration and the volume of residual disease following surgical resection. BOLD fMRI may be clinically useful for guiding extent of resection in diffuse gliomas.

Learning Objectives

By the conclusion of this presentation, participants should be able to (1) describe glioma-induced vascular dysregulation, (2) explain how the spatial extent of vascular dysregulation differs in IDH1 mutant and wild-type tumors, (2) discuss how BOLD fMRI may be used preoperatively as a biomarker of glioma infiltration.