Imaging Markers of Isocitrate Dehydrogenase-1 Mutations in Gliomas

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Glioblastomas (GBM) are the commonest and most aggressive primary tumor of the brain. They are associated with an appalling prognosis, with survival of a matter of weeks in untreated patients, improving to 14 to 16 months with radiotherapy with concomitant and adjuvant chemotherapy.[1,2] In this era of molecular biology, diagnosis still relies on the World Health Organization classification system, which only requires a tumor to have features of an astrocytic tumor with either necrosis or microvascular proliferation on light microscopy.[3] Yet, it is clear that GBMs form a very heterogeneous group of tumors. Although there are recognized histological variants (eg, giant-cell GBM, GBM with oligodendroglial differentiation), it is doubtful how useful this distinction is in predicting outcome.[4] It is clear that we need to be able to better subtype GBMs to consider individualizing treatment.

We have known for some time that GBMs can arise from 2 pathways: either as a primary de novo GBM or as a secondary GBM from a pre-existing low-grade glioma. These 2 subtypes have different mutations and activate different pathways within the cells.[5] The discovery of mutations of the isocitrate dehydrogenase (IDH) gene, an early marker of astrocytic tumor development,[6] has led to the realization that some GBMs have this mutation.[7-9] This cohort of patients has a far better prognosis, with a median survival of 31 months compared with 15 months in patients with wild-type IDH.[8]

IDH-1 MUTATIONS IN GLIOMAS

IDH exists in 2 major forms within cells: the cytosolic IDH-1 or the mitochondrial IDH-2. The normal role is to convert isocitrate from the Krebs cycle to α-ketoglutarate and in the process replenish NADPH and NADH. α-Ketoglutarate is also a cofactor for histone demethylase and is involved in regulation of the genome. It is thought that α-ketoglutarate provides a mechanism for cells to deal with oxidative stresses (eg, that produced by chemotherapy or radiotherapy). Mutations of the IDH gene result in failure to synthesize α-ketoglutarate; instead, it leads to the production of the oncometabolite 2-hydroxyglutarate (2-HG).[10] This results in the cell being unable to respond to oxidative stresses and may increase sensitivity to chemotherapy and radiotherapy. 2-HG also inhibits histone demethylases and can lead to the dysregulation of epigenetic and gene expression. In addition, 2-HG induces the hypoxia-inducible factor-1α subunit,[11] leading to alteration of tumor angiogenesis and growth in low oxygen concentrations.[12]

Mutations of the IDH gene are found in >80% of World Health Organization grade II and III gliomas[8] and in 12% of GBMs, mostly secondary GBMs.[7,8] In gliomas, the majority of mutations involve IDH-1 rather than IDH-2.[8] Examination of the mutation in gliomas has shown that these mutations are predominantly a point mutation of histidine replacing arginine in codon 132 (R132H mutation).[6,7] This can be detectable with an immunohistochemical test[13] that is able to identify most mutations very simply in paraffin-embedded specimens. Recent reviews of immunohistochemical diagnosis have suggested that it can identify IDH-1 mutations with a concordance rate to sequencing of 88% to 99%.[14]

If IDH-1 mutations can be identified in at least 90% of cases with a simple immunohistochemical test, is there a need to develop imaging methods to do this noninvasively? There are potential advantages:

1. IDH-1 mutation may influence surgical decision making. A recent study by Beiko et al[15] showed that IDH-1–mutated high-grade gliomas were more amenable to complete resection of enhancing tumor and had an improved survival with resection of the nonenhancing components.
2. Therapeutic blockade of IDH-1. There is much interest in developing selective inhibitors of the R132H IDH-1 mutation. Studies suggest that this slows tumor growth and promotes glioma differentiation in IDH-1–mutated tumors but not in IDH-1 wild-type tumors.[16]

IDH-1 MUTATIONS AND CONVENTIONAL MAGNETIC RESONANCE IMAGING

Studies comparing IDH-1 mutation status with conventional imaging have shown some differences between IDH-1–mutated and IDH-1 wild-type gliomas (Figure 1). IDH-1 tumors are more commonly found in the frontal lobe,[15,17-22] whereas IDH-1 wild-type tumors commonly involve the insular region.[23] IDH-1–mutated high-grade gliomas are more likely to be nonenhancing[17,19] and in those exhibiting enhancement may have a distinct enhancing border[23] although other studies suggest that this does not differentiate these tumors.[18] In anaplastic oligodendrogliomas, wild-type tumors are more likely to exhibit a ring-like contrast enhancement pattern.[20]

None of these features, however, are diagnostic. Carrillo et al[17] have shown that combining the presence of enhancement, tumor size, and the presence of cysts or satellite lesions can predict IDH-1–mutated gliomas with a sensitivity of 71.4% and specificity of 99%. This needs testing prospectively.

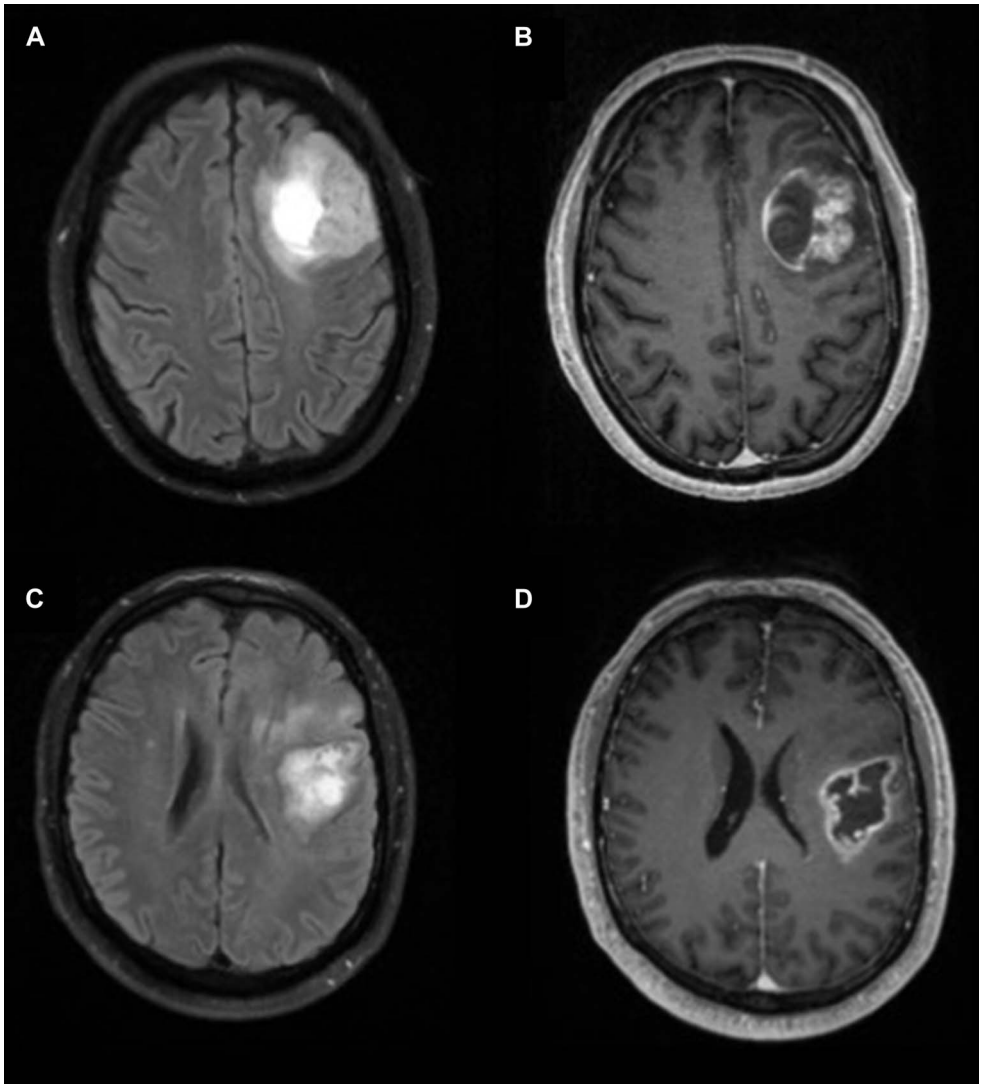

FIGURE 1. *A conventional magnetic resonance imaging (MRI) study of 2 patients. Top, the fluid-attenuated inversion-recovery (FLAIR) image (**A**) and contrast-enhanced T1-weighted MRI (**B**) of a patient with a glioblastoma with an isocitrate dehydrogenase-1 (IDH-1) mutation. Bottom, the tumor is located in the frontal lobe of this patient with a glioblastoma with wild-type IDH-1, but otherwise, there are few differences between the FLAIR image (**C**) and contrast-enhanced T1-weighted MRI (**D**).*

MEASURING 2-HG WITH MAGNETIC RESONANCE SPECTROSCOPY

As previously mentioned, IDH-1–mutated gliomas lead to accumulation of 2-HG within the tumor. Cell culture studies suggest a 100-fold increase in IDH-1–mutated cells to concentrations of 5 to 35 mmol/L,[10] a level similar to that detected with high-resolution magic angle spectroscopy of ex vivo biopsy specimens. A number of studies have shown that 2-HG can be detected in ex vivo biopsy specimens with high-resolution magic angle spectroscopy.[24-27] The concordance between detecting 2-HG and IDH-1 mutation status is 86.4%.[25] Detection of 2-HG identifies IDH-1 mutations with a sensitivity of 96% and specificity of 95.2%, giving an overall accuracy of 97.8%.[26] 2-HG levels within these biopsy specimens increase with increased tumor grade and increased MIB-1 proliferation rate.[25] It is negatively correlated with vessel density and ADC.[25] In progressive low-grade gliomas, an increase in 2-HG can identify glioma transformation to a higher grade.[27]

Recent studies have also shown that 2-HG can be detected in patients with gliomas using single voxel magnetic resonance spectroscopy (MRS).[24,28,29] These studies suggest that it can identify IDH-1 mutations with high sensitivity.[24,28,29] Large-scale validation studies are required to qualify this as a biomarker of IDH-1 mutation status.

The difficulty of identifying 2-HG with spectroscopy is that the spectrum for 2-HG occurs between 2.6 and 2.4 ppm, a region shared with glutamate, glutamine, and *N*-acetyl-L-aspartate. In fact, the spectrum overlaps the glutamate and glutamine peaks (Figure 2). Interestingly, the glutamate and glutamine peaks are not affected by the IDH-1 mutation status, suggesting that the differences are due to changes in 2-HG. Attempts using standard short-echo MRS methods have shown a high sensitivity but low specificity with a false-positive rate of 26%.[28] Longer-echo MRS methods that involve spectral editing and fitting the spectra to the 2-HG peak can improve the diagnostic ability[29] without adding too much complexity. More accurate and sensitive methods include different MRS techniques in which overlapping

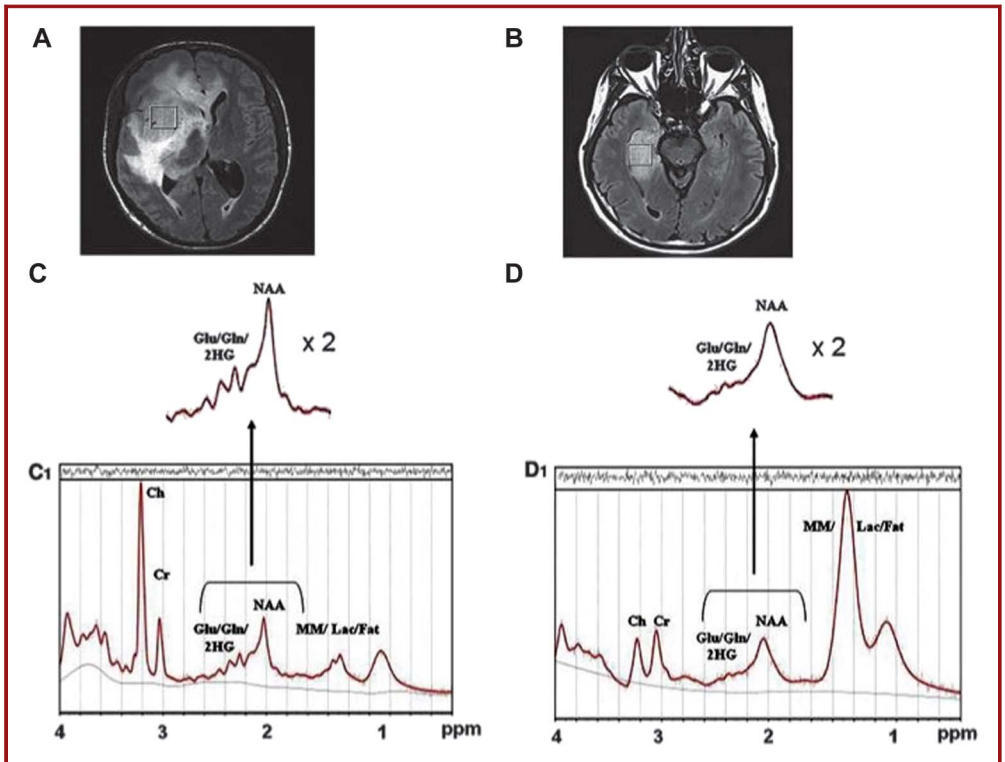

FIGURE 2. *A short-echo magnetic resonance spectroscopy study from 2 patients with anaplastic astrocytomas. The voxels examined in a patient with an isocitrate dehydrogenase-1 (IDH-1) mutation (A) and in a patient with a wild-type IDH-1 (B) show little differences on conventional imaging. The spectroscopic data showed that there is a detectable peak corresponding to 2-hydroxyglutarate (2-HG) that overlaps the glutamate (Glu)/glutamine (Gln) peaks in the IDH-1–mutated patient (C). This is not detected in the spectra of the IDH-1 wild-type patient (D). Gln, glutamine; Glu, glutamate; NAA, N-acetyl-L-aspartate; T1-w, T1-weighted. Reproduced from Pope et al[28] with permission from the publisher. Copyright © 2012 Springer International Publishing AG.*

resonances are removed[24,29] or a 2-dimensional correlation MRS method.[24] These methods have been used by some groups, but they are not standard methods and are difficult to apply on standard clinical machines. Overall, there is yet to be a consensus on the best method of measuring 2-HG that balances accuracy and ease of use to ensure that it becomes part of routine clinical practice.

IDENTIFYING CHANGES IN MICROSTRUCTURE WITH DIFFUSION AND DIFFUSION TENSOR IMAGING

Diffusion MR provides methods that can probe the microscopic physical properties of tissues and the influence of cellularity and patterns of cellular organization. The biophysical properties of diffusion imaging are reviewed elsewhere.[30]

Tan et al[31] investigated the role of diffusion and diffusion tensor methods to differentiate between IDH-1–mutated and IDH-1 wild-type astrogliomas. They found that grade II and III tumors have an increase in normalized apparent diffusion coefficient (ADC) and a reduction in normalized fractional anisotropy (FA) in the IDH-1–mutated tumors and postulated that this was due to differences in tumor cellularity and angiogenesis. They were able to calculate cutoff values for the ADC and FA that provided good sensitivity and specificity for determining the IDH-1 mutation status.

Diffusion tensor imaging has commonly been used to study the peritumoral region. Tan et al[31] found no difference in these markers in the peritumoral regions, but previous studies have shown that FA is an insensitive marker for identifying the invasive margin.[32] Using a tensor decomposition method splits the information in the diffusion tensor into an isotropic component (which measures magnitude of diffusion) and anisotropic component (which is sensitive to directionality of diffusion).[33,34] Our previous studies have shown that these methods can identify 3 invasive phenotypes that predict the pattern of tumor progression[35] and time to tumor progression.[36] In a cohort of GBM patients, virtually all of the IDH-1–mutated tumors as detected with R132H immunohistochemistry exhibited a minimally invasive phenotype, whereas only 8% of IDH-1 wild-type tumors exhibited this phenotype[37] (Figure 3). This suggests different invasive behaviors between IDH-1–mutated and wild-type tumors. These may explain the differences in survival seen with extended resection of IDH-1–mutated tumors.[15]

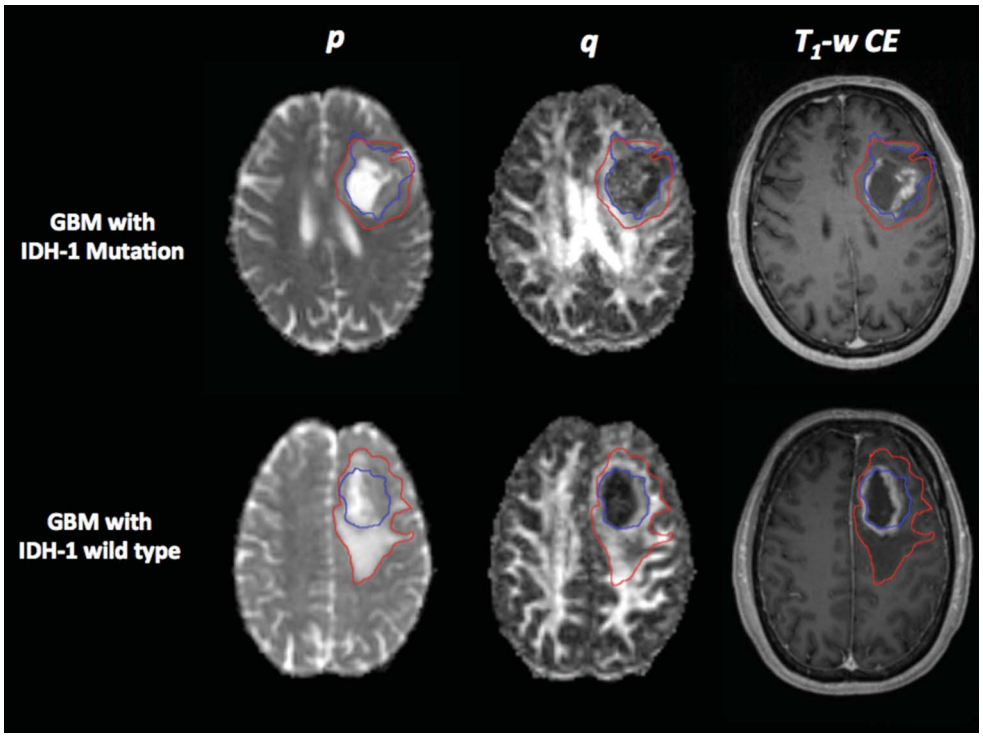

FIGURE 3. *An example of the diffusion tensor tissue signatures of 2 patients with glioblastomas. Both are 46-year-old men with left frontal glioblastomas. Top, a patient with an isocitrate dehydrogenase-1 (IDH-1) mutation. There is little difference (<1 cm) between the p (isotropic) and q (anisotropic) components of the diffusion tensor, suggesting a minimally invasive phenotype. Bottom, a patient who has an IDH-1 wild-type glioblastoma. There is clear evidence of a diffuse pattern of invasion.*

CONCLUSION

IDH-1–mutated gliomas are an important subgroup of gliomas with an improved prognosis. Imaging methods, particularly spectroscopic and diffusion, are able to identify this subgroup. Further studies are required to prospectively assess these biomarkers in a multicenter setting to allow their use in routine clinical practice.

Disclosures

Dr Price is supported by a Clinician Scientist Fellowship from the National Institute of Health Research. The author has no personal, financial, or institutional interest in any of the drugs, materials, or devices described in this article.

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