Isocitrate dehydrogenase mutations
A biomarker for glioma-related excitability and seizures

Tumor-related epilepsy (TRE) is common in patients with gliomas (40%-70%) and carries a substantial degree of morbidity and mortality.1,2 The impetus to understand the pathophysiology of TRE has led to the identification of several tumor markers that are associated with increased risk of seizures. Tumor-mediated glutamate release is one proposed mechanism that has more recently gained traction.3,4 Another tumor marker that has attracted the attention of researchers is expression of mutated isocitrate dehydrogenase 1 (IDH1mut), an enzyme whose normal function is key to the Kreb cycle; the non-mutated enzyme catalyzes the conversion of isocitrate to &kappa;etoglutarate. IDH1mut is an accepted diagnostic biomarker for secondary glioblastomas that is associated with improved survival.5 In its mutated form, IDH1mut reduces &kappa;etoglutarate to D-2-hydroxyglutarate (D2HG). Structural similarities between D2HG and glutamate have promoted the theory that overproduction of D2HG could mechanistically play a role in neuronal excitation in the glial tumor model. Thus far, the association between mutant IDH expression and epilepsy has been disputed in the work of previous groups.6,7

In this issue of Neurology®, Chen et al.8 reexamined the association between IDH1mut and seizure risk in patients with glial tumors. Their approach is both epidemiologic and translational, through the use of multielectrode array (MEA) recordings. First the authors employed a case-control design, retrospectively analyzing independent cohorts of patients with glial tumors (WHO grade II–IV) from 3 institutions. They evaluated for an association between IDH1mut expression and the presence of seizures prior to surgery. Patients whose tumors expressed IDH1mut were 25%-75% more likely to have experienced seizures at diagnosis than patients with wild-type IDH1 expression. Multivariate analysis showed that the increased risk associated with IDH1mut was independent of several other relevant potential risk factors (i.e., tumor location, 1p/19q deletion, WHO grade).

This epidemiologic work utilizes a large sample of patients from 3 separate institutions across the country, allowing for a reasonable amount of generalizability to the results. Certain limitations to this approach must be recognized. As noted by the authors, determination of seizure activity at presentation through retrospective analysis of medical records is not the most precise determinant of outcome status. On one hand, patients experiencing focal seizures with nonmotoric symptoms at presentation may not be diagnosed with seizures. Alternatively, patients with nonepileptic focal symptoms may be incorrectly diagnosed with symptomatic seizures. Although potentially helpful in distinguishing epileptic vs nonepileptic phenomena, diagnostic EEG data are typically not available. This is a recurrent problem in retrospective cohort studies in TRE and has the potential of introducing misclassification bias.

In order to establish a direct excitatory role for D2HG, the second phase of this study involved in vitro measurement of firing rate of rat cortical neurons using MEA recordings. Exposure to exogenous D2HG resulted in an increased duration of synchronized network burst firing, a finding that was subsequently blocked by a selective NMDA antagonist. This finding suggests that D2HG increases neuronal activity in this paradigm, and may do so via the NMDA receptor. Additional limitations should be noted for this portion of the study. While an acceptable test for network hyperexcitability, MEA recordings have not been established as a valid model for epilepsy and are a potentially weak test for determining proconvulsant activity of D2HG. Such activity would have been supported through single electrode recordings of D2HG-generated bursts of action potentials recorded from neurons or direct recordings of D2HG-evoked currents. Although this work implicates NMDA-mediated activity as the main excitatory conduit for D2HG, there is insufficient evidence to exclude other receptor activation (e.g., AMPA) as a cause for hyperexcitability. The authors recognize these limitations and that these data warrant further investigation including single-electrode recordings and in vivo models.
IDH<sup>mut</sup> expression and generation of seizures may be linked in ways besides activating glutamate receptors. The efficacy of a ketogenic diet has long suggested a role for the Kreb cycle in the treatment of seizures; the hypothesized mechanism involves bypassing glycolysis and depending on fatty acids and ketones for energy metabolism. Neurons have high energy demand and limited energy stores and lactate supplied by astrocytes helps meet this gap.<sup>9</sup> Recent data suggest that inhibition of lactate dehydrogenase reduces epileptiform activity, which is reversed by pyruvate.<sup>10</sup> IDH<sup>mut</sup> expression may inhibit the Kreb cycle and reduce lactate production, forcing neurons to depend on glycolysis to generate energy and elevate pyruvate levels, which may promote neuronal depolarization and seizures. This mechanism has not been tested.

This work has potential clinical implications. The treatment of TRE relies on the use of antiepileptic drugs (AEDs). A large proportion of those with TRE are refractory to standard AEDs.<sup>1</sup> Many available newer generation AEDs have novel or selective mechanisms of action previously not tested in this patient population. An ongoing study (NCT02363933) hopes to assess the efficacy of perampanel, a noncompetitive AMPA agonist, as adjunctive therapy in patients with primary glioma. Furthermore, selecting agents tailored to act against known tumor-specific pathophysiologic mechanisms could enhance treatment value. New agents specifically designed to target novel mechanisms of action implicated here (e.g., IDH1<sup>mut</sup>, X<sub>c</sub>-cysteine-glutamate transporter) are currently under early stage development. Prophylactic AED therapy in seizure-naive patients with gliomas is controversial. Only a handful of well-designed Class I studies have been conducted to test the efficacy of AED prophylaxis in this patient population, and most of these studies used older AEDs (e.g., phenytoin).<sup>11</sup> Using this limited evidence, the American Academy of Neurology's 2000 practice parameter recommended against prophylaxis in seizure-naive patients with brain tumors.<sup>12</sup> Their meta-analysis failed to demonstrate efficacy of AED prophylaxis and identified a heightened risk of AED-associated toxicities. Future trials may benefit from targeting patients at high risk of developing TRE (i.e., prognostic enrichment) utilizing results from this and similar work.

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**REFERENCES**