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Molecularly determining cognition in glioma: New insights as the plot thickens

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The World Health Organization's (WHO) 2021[1] update classifying CNS tumors, signaled a full transition into the molecular era of clinical care for patients with diffuse glioma. As we lean into this molecular world and allow it to deepen our knowledge of gliomagenesis and progression, we have an opportunity to integrate these findings into our understanding of cancer-induced neurological and cognitive impairments.[2] By better understanding the molecular alterations that lead to functional impairments caused by both cancer and cancer-directed therapies, we can hope to identify new treatments for improving cognitive and patient-reported outcomes in glioma.

Wefel et al[3] were among the first to publish correlations between diffuse glioma subtype and cognition. They observed isocitrate dehydrogenase (IDH) wildtype tumors correlated with worse cognitive outcomes, including more severe impairments in learning and memory, processing speed, language, and executive functioning compared to their IDH-mutated counterparts. They highlighted lesion momentum (or speed of tumor growth) as a potential mechanism for differing cognitive impairments between groups.

van Kessel et al[4] have extended these findings by analyzing tumor molecular characteristics beyond those required for subclassification. In this edition of *Neuro-Oncology*, they present their work on a cohort of several hundred patients with gliomas to investigate not the prognostic and predictive impact of tumor molecular characterization, but rather explore correlations with cognition.

Their exploratory approach uncovered 19 genes with potential importance for cognitive functioning. They first screened molecular drivers, identifying 11 genes of interest using unsupervised gene set enrichment assay (GSEA) analysis from 65 surgical patient samples. Wisely, given the exploratory nature of this study and relatively small sample size, they added to their risk model known molecular determinants of glioma invasion, neuronal activity-dependent proliferation, and metabolism, including IDH, ATRX, BDNF, and NLGN3. They went on to analyze all 19 genes by tissue microarray and immunohistochemistry in a larger sample of 197 surgical glioma cases with preoperative neuropsychological testing. They found several intriguing correlations with cognitive domains of psychomotor speed, memory, and executing functioning. They concluded the role of glioma biology was possibly an independent correlate of cognitive dysfunction above traditional clinical factors, such as location, volume, and grade. Moreover, these findings may have important implications for clinical care.

Those of us who directly care for adults with diffuse gliomas are keenly aware of the importance cognitive outcomes have on the quality of life of our patients and their caregivers. And we are also all too familiar with how difficult it can be to predict the cognitive trajectory of an individual patient. Molecular characterization and the tumor microenvironment's role in glioma proliferation are starting to influence therapeutic choices and response to treatment. Additionally, advances in functional imaging, such as connectomics and resting-state MRI, present opportunities to integrate tumor molecular characterizations and identify biomarkers for cognition in patients with glioma.[5] The work by van Kessel et al[4] and other works from this group again shines a light on the power of perioperative cognitive testing, regardless of tumor location, particularly for patients with non-enhancing tumors which are likely to be IDH-mutant.[6,7]

What is not addressed in this manuscript? First, while this excellent study uncovered tumor-driven factors that correlate with cognitive outcomes, their experimental model did not include a model for prediction. Furthermore, their cross-sectional design allowed identification of impairments at the time of diagnosis, when perhaps the bigger question is the longer-term cognitive impact. The role of cognitive molecular drivers, during and after treatments, such as radiotherapy and chemotherapy, remains a critically important question. For many patients, a short-term decline in neurological and cognitive function may be palatable,

while a progressive decline over years or decades could be a bigger concern. There is a real need to identify biomarkers to predict cognitive decline and recovery after surgery, radiotherapy, and chemotherapy. Who is likely to have severe cognitive impairment within 5 years of radiotherapy vs not? Unfortunately, longitudinal cognitive assessments in patients with glioma are not standard of care in the United States, and patient attrition and heterogeneity in testing batteries, timing of assessments, and tumor diagnoses and treatments hinder our ability to generalize study results.[8,9] To truly understand molecular determinants of cognition, we need longitudinal data.

Additionally, as more treatments, particularly in IDH-mutant gliomas, become available and survival improves, we must forge a better understanding of how molecular markers impact cognition to better inform our conversations around type and timing of treatment. There is also a need within ongoing and future clinical trials, again particularly those in IDH-mutant gliomas, to prioritize cognitive and patient-reported outcomes, in addition to progression-free survival and overall survival. More treatment options for our patients remain our shared dream, but without a prospective and systematic understanding of how these different choices impact the lives of our patients, we run the risk that these conversations are incomplete.

The work from van Kessel et al[4] is also a significant step toward identifying tumor-specific genetic alterations that may translate into opportunities to improve cognition, mirroring a precision medicine approach to shape quality of life and related cognitive outcomes for patients with glioma. This paves the way for more tailored pharmacologic interventions, but also in the blossoming fields of cognitive rehabilitation, other neurorehabilitation approaches, such as repetitive transcranial magnetic stimulation (rTMS),[10] and lifestyle modification approaches, such as exercise. Access to experienced rehabilitation neuropsychologists and exercise physiologists is often a limited resource and identifying cognitive prognostic factors could be of great value.[9]

These may feel like daunting tasks, and will certainly require international collaborations to generate datasets large enough to harness the power of machine learning to untangle the inevitable heterogeneity and efficacy of developing treatments. However, the authors of this study are congratulated for providing foundational work that moves the field closer to the goal of giving our patients with glioma better, not just longer, lives.

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