WriteClick: Editor's Choice

Editors' Note: Is synthetic cannabis more likely than pure cannabis to be associated with stroke? McSherry raises an interesting question. Chamberlain points out that the glioma biomarker *ATRX* (α-thalassemia/mental retardation syndrome X-linked) gene was not mentioned in the study by Wick et al. on the value of methylguanine methyltransferase (*MGMT*) in gliomas. The authors respond and discuss the role of *ATRX* and its interaction with *MGMT* and *IDH1* (isocitrate dehydrogenase 1).

—Chafic Karam, MD, and Robert C. Griggs, MD

SPICE, POT, AND STROKE

Joseph W. McSherry, Burlington, VT: In the last paragraph of his editorial, Dr. Brust[1] seemed doubtful of anecdotal reports of stroke in marijuana users, given common cannabis usage and lack of reports. Freeman et al.[2] reported 2 persons using spice with associated vascular events. In the future, it will be important to clarify when a stroke in a cannabis user may be due to use of synthetic CB1 agonists. The paucity of cannabis stroke articles in the 1960s and 1970s contrasts to recent articles showing enhanced stroke risk in "cannabis" users. Those using both the natural plant and synthetic forms may be at risk as the synthetic form is not detected on typical drug screens. The unavailability of pure cannabis may lead to increased strokes and a public health problem.

1. Brust JC. Spice, pot, and stroke. Neurology 2013;81:2064–2065.
2. Freeman MJ, Rose DZ, Myers MA, Gooch CL, Bozeman AC, Burgin WS. Ischemic stroke after use of synthetic marijuana "spice." Neurology 2013;81:2090–2093.

PROGNOSTIC OR PREDICTIVE VALUE OF *MGMT* PROMOTER METHYLATION IN GLIOMAS DEPENDS ON *IDH1* MUTATION

Marc C. Chamberlain, Seattle: Wick et al.[1] determined that the interaction of molecular markers (methylguanine methyltransferase [*MGMT*], isocitrate dehydrogenase 1 [*IDH1*], and loss of chromosomes 1p and 19q) in anaplastic gliomas (AG) was a hypothesis-generating analysis. This is because examination of interactive biomarkers was never prespecified as an endpoint in the NOA-04 trial.[2]

Biomarker determination segregates AG into 2 categories based on presence or absence of 1p19q codeletion.[3] *MGMT* methylation or *IDH1* mutation does not modify the prognostic and predictive value of 1p19q codeletion. The suggested interaction is novel between *IDH1* and *MGMT* in the larger cohort of AG that is not codeleted. In *IDH1* wild-type AG, patients with *MGMT* promoter methylation derive greater benefit from temozolomide, whereas patients without *MGMT* methylation derive greater benefit from radiotherapy.[4]

The authors did not mention the glioma biomarker *ATRX* (α-thalassemia/mental retardation syndrome X-linked) gene, which regulates chromatin remodeling. It is mutated in gliomas of astrocytic lineage, is mutually exclusive with 1p19q codeletion, and may be both prognostic and predictive.[5] Determining the interaction of *ATRX* with *IDH1* and *MGMT* will provide further insight into the utility of these glioma biomarkers.

Author Response: Wolfgang Wick, Michael Platten, Heidelberg; Guido Reifenberger, Düsseldorf, Germany; Michael Weller, Zurich: In the NOA-04 biomarker cohort, loss of ATRX expression is seen in anaplastic astrocytomas (45%) (AA), oligoastrocytomas (AOA) (27%), and oligodendrogliomas (AO) (10%). It is mainly restricted to *IDH* mutant tumors and almost mutually exclusive to the 1p/19q codeletion.[6] It is inversely correlated with hotspot mutations in the promoter region of telomerase reverse transcriptase (*TERT*).[7]

ATRX may be suitable to regroup AOA into 2 distinct entities with favorable prognosis. Clinically, AOA with *ATRX* loss are similar to AA with good prognosis, whereas AOA carrying 1p/19q codeletion are indistinguishable from AO. AA with the *IDH* mutation are further stratified by *ATRX*, with the loss providing a better prognosis.[6]

While fitting these data into the interaction term used for the *MGMT/IDH* analysis[1] is formally restricted due to the high number of necessary events for this triple interaction, we see a need for *IDH* testing in AG. For clinical decision-making, we assess O6-*MGMT* status

in the *IDH* wild-type group. In the *IDH* mutated group, the *ATRX* status allows a prognostic subclassification. These markers plus 1p/19q codeletion argue for a molecularly based definition of all AG, with AOA no longer considered as a separate category.

1. Wick W, Meisner C, Hentschel B, et al. Prognostic or predictive value of *MGMT* promoter methylation in gliomas depends on *IDH1* mutation. Neurology 2013;81:1515–1522.
2. Wick W, Hartmann C, Engel C, et al. NOA-04 randomized phase III trial of sequential radiochemotherapy of anaplastic glioma with procarbazine, lomustine, and vincristine or temozolomide. J Clin Oncol 2009;27:5874–5880.
3. van den Bent MJ, Brandes AA, Taphoorn M, et al. Adjuvant provarbazine, lomustine and vincristine chemotherapy in newly diagnosed anaplastic oligodendroglioma: long-term follow-up of EORTC Brain Tumor Group Study 26951. J Clin Oncol 2013;31:344–350.
4. Wick W, Platten M, Meisner C, et al; NOA-08 Study Group of Neuro- oncology Working Group (NOA) of German Cancer Society. Temozolomide chemotherapy alone versus radiotherapy alone for malignant astrocytoma in the elderly: the NOA-08 randomised, phase 3 trial. Lancet Oncol 2012;13:707–715.
5. Jiao Y, Killela PJ, Reitman ZJ, et al. Frequent ATRX, CIC, FUBP1 and IDH1 mutations refine the classification of malignant gliomas. Oncotarget 2012;3:709–722.
6. Wiestler B, Capper D, Holland-Letz T, et al. ATRX loss refines the classification of anaplastic gliomas and identifies a subgroup of IDH mutant astrocytic tumors with better prognosis. Acta Neuropathol 2013;126:443–451.
7. Koelsche C, Sahm F, Capper D, et al. Distribution of TERT promoter mutations in pediatric and adult tumors of the nervous system. Acta Neuropathol 2013;126:907–915.

CORRECTION

A Survey of Cluster Headache (CH) Sufferers Using Vitamin D3 as a CH Preventative (P1.256)

In the abstract "A Survey of Cluster Headache (CH) Sufferers Using Vitamin D3 as a CH Preventative (P1.256)" by Peter Batcheller (*Neurology* 2014;82:P1.256), there is an error in the disclosures. It should have read: "Mr. Batcheller has nothing to disclose." The AAN staff regrets the error.

Author disclosures are available upon request (journal@neurology.org).

Prognostic or predictive value of *MGMT* promoter methylation in gliomas depends on *IDH1* mutation

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