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Neurology [ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Treatment of Glioblastoma in Elderly Patients

By Rajiv S. Magge, MD

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Dr. Magge reports no financial relationships relevant to this field of study.

SYNOPSIS: In a retrospective cohort study of elderly patients with glioblastoma, overall survival was superior with combined-modality therapy (radiation and chemotherapy) compared with chemotherapy alone or radiation alone.

SOURCE: Rusthoven CG, Koshy M, Sher DJ, et al. Combined-modality therapy with radiation and chemotherapy for elderly patients with glioblastoma in the temozolomide era: A National Cancer Database analysis. *JAMA Neurol* 2016; May 23. doi: 10.1001/jamaneurol.2016.0839. [Epub ahead of print].

More than half of patients with glioblastoma (GBM) are at least 65 years of age at presentation. Unfortunately, these elderly patients tend to have a poorer prognosis, potentially related to poor performance status, medical comorbidities, increased vulnerability to drug side effects, polypharmacy, and less aggressive goals of care. The landmark EORTC-NCIC trial established the standard-of-care treatment for GBM, consisting of concurrent radiation and temozolomide chemotherapy followed by adjuvant chemotherapy.[1] However, individuals older than 70 years of age were excluded from that trial. Since that time, there has been extensive controversy regarding the optimal management of elderly GBM patients. It is not clear whether this population should receive radiation therapy (RT), chemotherapy (CT), or combined-modality therapy (CMT, both radiation and chemotherapy).

In a retrospective cohort study, Rusthoven et al queried the National Cancer Database (NCB) for elderly patients (≥ 65 years old) with newly diagnosed GBM between 2005 and 2011, collecting complete data sets that included any RT, CT, tumor resection, Charlson-Deyo comorbidity scores, age, sex, and year of diagnosis. Survival of the treatment cohorts (RT alone, CT alone, or CMT) was estimated using the Kaplan-Meier method

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and further analyzed using the log rank test, univariate and multivariate Cox models, and propensity score-matched analyses.

The group identified 16,717 patients at least 65 years of age with newly diagnosed GBM in the NCB. The median age was 73 years and 8,870 (53%) were male. At presentation, 5,337 (32%) underwent biopsy only to establish diagnosis while 11,380 (68%) had some type of tumor resection. In terms of treatment, 8,435 (50%) patients received CMT (i.e., both RT and CT), 1,693 (10%) received RT alone, 1,018 (6%) received CT alone, and 5,571 (33%) received no therapy (best supportive care). CMT administration was observed more frequently in the setting of tumor resection, younger age, male sex, white race, lower comorbidity scores, and during the later years of the study.

The median overall survival (OS) by treatment cohort was 9.0 (95% confidence interval [CI], 8.8-9.3) months with CMT, 4.7 (95% CI, 4.5-5.0) months with RT alone, 4.3 (95% CI, 4.0-4.7) months with CT alone, and 2.8 (95% CI, 2.8-2.9) months with no therapy ($P < 0.001$). CMT remained superior to all the other groups on multivariate survival analyses, which adjusted for tumor resection, comorbidity scores, age, sex, race, and year of diagnosis. No significant difference in survival was observed between CT alone and RT alone, which were both superior to no therapy. The survival advantage for CMT over single-modality therapy was consistent within subgroup analyses, which stratified patients by age and tumor resection.

■ COMMENTARY

This large retrospective cohort study of patients queried from the NCB demonstrated improved overall survival with combined radiation therapy and chemotherapy for GBM in patients at least 65 years of age. Unfortunately, even with these data, the exact standard of care for older patients is still controversial. As acknowledged by the authors, a significant limitation of the study was the lack of O^6-methylguanine-DNA methyltransferase (MGMT) promoter methylation status of the tumors within the database. MGMT is a DNA repair enzyme that repairs DNA alkylation, which may make cancers less susceptible to DNA-alkylating agents such as temozolomide. Several studies have shown that patients with tumors that are MGMT hypermethylated (i.e., less functioning MGMT enzyme) have significantly improved survival with the addition of chemotherapy. As the status of MGMT methylation is unclear, it could be responsible for the different survival outcomes across the cohorts. Another important limitation of the study is the absence of data regarding performance status, which can carry heavy weight regarding prognosis and treatment efficacy.

On presentation, maximal safe resection with preservation of neurologic function (instead of biopsy) is generally preferred, but this, of course, depends on tumor location/size, goals of care, and other medical comorbidities. After surgery, the combination of both radiation therapy and chemotherapy can carry significant toxicity, but is probably indicated in patients with suitable performance status and good overall health. Shorter courses of hypofractionated radiation therapy have been shown to be better tolerated than standard regimens in older GBM patients with similar survival. Further, radiation alone may be an effective alternative in patients with unmethylated MGMT tumors, poor functional status, or significant medical problems. Conversely, emerging data support the use of temozolomide monotherapy in frail elderly patients with MGMT-methylated tumors.

The optimal treatment of GBM in older patients continues to be clarified. The field eagerly awaits new data, including the results of the EORTC-NCIC Phase III trial, which will compare the outcomes of elderly patients treated with RT and temozolomide chemotherapy vs. RT alone in a randomized fashion. ■

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ABSTRACT & COMMENTARY

Do Miller Fisher Syndrome, Guillain-Barré Syndrome, and Bickerstaff Encephalitis Overlap?

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports no financial relationships relevant to this field of study.

SYNOPSIS: All three of these syndromes — Miller Fisher, Guillain-Barré, and Bickerstaff encephalitis — occur following an acute gastrointestinal infection, with many cases of overlap syndromes, and deficits may progress during the first few days of illness.

SOURCE: Sekiguchi Y, Mori M, Misawa S, et al. How often and when Fisher syndrome is overlapped by Guillain-Barré syndrome or Bickerstaff brainstem encephalitis. *Eur J Neurol* 2016;23:1058-1063.

Initially reported in 1951 as "mesencephalitis and rhombencephalitis" by Bickerstaff and Cloake, patients with Bickerstaff brainstem encephalitis (BBE) presented with external ophthalmoplegia, ataxia, and altered consciousness, and recovered well, spontaneously. In 1956, Miller Fisher reported patients with external ophthalmoplegia, ataxia, and areflexia, also noting spontaneous recovery, with both papers noting a similarity to Guillain-Barré syndrome (GBS). With the finding, in 1992, of IgG anti-GQ1b antibodies in both BBE and Miller Fisher syndrome (MFS), the clinical spectrum of Fisher-Bickerstaff syndrome was created. How often does MFS overlap with BBE or GBS, and what is the clinical progression of one to the other?

Retrospective record review of 60 consecutive patients with MFS, seen between 1990-2014, at Chiba University Hospital, Chiba, Japan, was undertaken. All patients demonstrated the triad of external ophthalmoplegia, ataxia, and areflexia, with some patients noting additional pharyngeal-cervical-brachial (PCB) weakness. Pure MFS was defined as the presence of the triad, without pharyngeal, neck, or limb weakness. MFS/BBE was diagnosed if MFS patients developed alteration of consciousness, whereas MFS/GBS was diagnosed if they developed weakness of arms and legs. If only arm, pharyngeal, or neck weakness developed, MFS/PCB-GBS was diagnosed. All patients underwent nerve conduction studies and serum ganglioside antibodies measurements within two weeks of MFS onset, and patients were followed for at least six months or until disease remission. Statistical analysis comprised Chi square or Fisher's exact test, analysis of variance with Bonferroni correction, and Dunnett's test.

Among the 60 MFS patients, 50% (n = 30) remained purely MFS throughout their course, with the remaining 50% demonstrating an overlap of PCB-GBS in 23% (n = 14), GBS in 15% (n = 9), or BBE in 12% (n = 7). Progression from onset of MFS to these overlap syndromes developed in five, three, and three days, respectively. Incidence of prior infection, age of disease onset, and ganglioside positivity, including anti-GQ1b, was not statistically different between the groups. Overlap of MFS with BBE or GBS develops in 50% of cases, and does so within seven days, but cannot be predicted at first evaluation.

■ COMMENTARY

Combined IgG and IgM anti-GQ1b antibodies have been reported in two childhood cases, ages 4 and 6 years, of acute isolated bilateral ophthalmoplegia occurring shortly after *Campylobacter jejuni* enteritis.[1] Neither child demonstrated weakness, ataxia, or deep tendon reflex abnormality. However, in a larger study encompassing 21 patients with acute ophthalmoplegia (AO), 13 with optic neuritis (ON), and 12 with MFS, none of the ON patients and only one with AO was found to have elevated GQ1b titers, compared to 11/12 with MFS.[2] GQ1b was present in the cerebrospinal fluid (CSF) of two of 10 MFS patients tested, but in none of those with AO or ON. Serum GQ1b positivity is specific for MFS, but its role in AO and ON is speculative. CSF measurement of GQ1b adds nothing. Still unanswered is whether these antibodies are directly pathogenic, or an epiphenomenon, resulting from disruption of the nerve sheath with exposure of hitherto hidden antigens to immune surveillance and autoantibody production. ■

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2. Spatola M, Du Pasquier R, Schleup M, et al. Serum and CSF GQ1b antibodies in isolated ophthalmologic syndromes. *Neurology* 2016;86;1780-1784.

ABSTRACT & COMMENTARY

Greater Weight Loss Later in Life Is Associated with Increased Risk of Mild Cognitive Impairment

By Makoto Ishii, MD, PhD

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Dr. Ishii reports no financial relationships relevant to this field of study.

SYNOPSIS: In a population-based, prospective study of subjects 70 years of age or older, increasing weight loss per decade from midlife to late-life was associated with an increased risk of incident mild cognitive impairment.

SOURCE: Alhurani RE, Vassilaki M, Aakre JA, et al. Decline in weight and incident mild cognitive impairment: Mayo Clinic Study of Aging. *JAMA Neurol* 2016;73:439-446.

Alzheimer's disease (AD) currently remains an incurable disease. Identifying people with increased risk or with the earliest clinical manifestations of AD could have significant impact on finding new strategies for the prevention and treatment of AD. Mild cognitive impairment (MCI) is an early prodromal stage of dementia, where every year approximately 5% to 15% of persons with MCI will progress to dementia. Previously, weight loss has been reported to increase dementia risk and precedes the cognitive decline, but it remains unclear if greater weight loss from midlife to late-life is a prodromal manifestation of dementia that is associated with incident MCI.

Therefore, the study authors investigated whether greater weight loss was associated with incident MCI using participants from the Mayo Clinic Study of Aging, an ongoing, prospective, population-based study initiated on October 1, 2004. Eligible subjects, who were 70 to 89 years of age at study initiation and without dementia or in hospice care, were recruited randomly and had follow-up evaluations every 15 months. Inclusion criteria included normal cognition at baseline evaluation, at least one follow-up evaluation, and data available on maximum weight and height in midlife. All participants were administered the Clinical Dementia Rating Scale and the Functional Activities Questionnaire, and underwent extensive neuropsychological and neurological evaluation. A diagnosis of MCI, dementia, or normal cognition was made by consensus. Body mass index (BMI) was computed from the measured height and weight at each evaluation, and the maximum weight and height in midlife were determined from the medical records of each participant. At the baseline visit, all demographic variables, medical history, smoking and alcohol use, and apolipoprotein E ε4 (APOE4) carrier status by genotyping were obtained.

Of the 1,895 cognitively normal participants at baseline (50.3% men; mean age, 78.5 years), 524 (27.7%) participants developed incident MCI over a mean follow-up of 4.4 (standard deviation, 2.4) years. Participants who developed MCI were older, more likely to be APOE4 carriers, and more likely to have diabetes, hypertension, or coronary artery disease compared with those participants who remained cognitively normal. Furthermore, the mean weight change was greater for those who developed incident MCI than those who remained cognitively normal (-2.0 [5.1] vs. 1.2 [4.9] kg; $P = 0.006$). Men who developed incident MCI had greater mean loss of weight per decade than men who did not (-2.1 [5.3] vs. -1.0 [4.6]; $P = 0.02$), but there was no significant difference in women (-1.9 [4.8] vs. -1.5 [5.3]; $P = 0.12$).

After adjusting for sex, education, and APOE4 carrier status, a greater decline in weight from midlife was associated with an increased risk of incident MCI (hazard ratio [HR], 1.04; 95% confidence interval, 1.02-1.06; $P < 0.001$). A weight loss of 5 kg/decade corresponded to a 24% increased MCI risk (HR, 1.24). Additionally, adjusting simultaneously for potential confounding factors such as alcohol problems, depressive symptoms, statin use, diabetes, hypertension, coronary heart disease, cigarette smoking, and stroke, still resulted in the same association between weight change and MCI. The effect sizes were greater in men than in women, but they were significant in both sexes. Interestingly, the association between weight loss and MCI was consistently seen, regardless of whether the participants were underweight, normal weight, overweight, or obese at midlife.

■ COMMENTARY

This study is consistent with other prospective studies that found a correlation between weight loss and increased dementia risk. Importantly, the study authors hypothesized that weight loss may represent a prodromal

or early manifestation of MCI, and, therefore, weight loss should be seen regardless of midlife weight. Overall, the study findings were consistent with this hypothesis and provide further evidence that weight loss is an early clinical manifestation of AD.

The strength of this paper is that it is a well-designed prospective population study with a relatively large cohort that had the ability to assess body weights from medical records of the participants for midlife and from direct measurements in late-life. Therefore, this study avoided confounding factors that may be present in other studies, such as lack of clarity on age at assessment of weight, BMI, and onset of dementia. A limitation of this study is that the diagnosis of MCI or dementia was based on a clinical diagnosis rather than on established pathological markers, leaving the possibility for misclassification. Another limitation is that it was not possible to determine whether the weight loss was intentional or unintentional, although the consistent association of weight loss with incident MCI across all midlife weight classes suggests that it is likely unintentional.

Finally, this study could not address the causal mechanism of the weight loss in prodromal stages of dementia. It is speculated that dysfunction in factors that regulate body weight, such as leptin and other hormones, could contribute. Alternatively, amyloid and/or tau deposition in brain regions that control appetite and/or systemic metabolism, such as the hypothalamus or olfactory bulb, could play a role in the weight loss. Future investigations using molecular approaches in mouse models and well-designed human studies are likely to help elucidate the mechanisms underlying weight loss in AD, which may eventually lead to the development of new diagnostic and therapeutic approaches against AD. ■

ABSTRACT & COMMENTARY

Blood-Based Biomarkers in the Evaluation of Alzheimer's Disease

By Michael T. Lin, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Lin reports no financial relationships relevant to this field of study.

SYNOPSIS: At the present time, no blood-based biomarkers have been identified as reliable indicators of A-beta amyloid deposition in the brain.

SOURCE: Khan AT, Dobson RJB, Sattlecker M, et al. Alzheimer's disease: Are blood and brain markers related? A systematic review. *Ann Clin Transl Neurol* 2016;3:455-462.

Lack of an easy biological test for Alzheimer's disease (AD) is a barrier to early diagnosis, entry into trials, and initiation of treatment. Currently available biological tests (amyloid PET or CSF A-beta and tau measurement) are expensive and/or invasive, so there is considerable interest in developing a blood test. Unfortunately, as reviewed recently by Khan and colleagues, there is still a long way to go.

The authors began by searching PubMed for studies of protein markers in AD brains, looking for discovery-based (as opposed to candidate-based) proteomic studies not focused on post-translational modifications. They found only 11 such studies, and of the 371 proteins identified across these studies, only three proteins (heat shock cognate 71 kDa protein, ubiquitin C-terminal hydrolase L1, and 2',3'-cyclic nucleotide 3'-phosphodiesterase) were found in multiple studies, with a consistent direction of change in all studies that identified them.

Next, the authors compared 176 blood proteins that they had found in a previous review[1] to the 371 brain proteins identified, and found 18 overlaps between blood and brain. However, only one overlap, complement C4a, occurred multiple times in both blood and brain studies.

■ COMMENTARY

As noted within the article, these results are extremely preliminary, at best. There is no clear relationship between any of the proteins mentioned above (HSC71, UCHL1, CNP, C4a) and A-beta and tau; moreover, none of the brain studies reviewed identified A-beta or tau. It is encouraging that this review found some overlap (C4a) between blood and brain studies. The specific finding of a complement protein agrees with recent studies showing an AD blood profile dominated by complement proteins.[2] Moreover, a recent laboratory study suggests that complement plays a role in loss of synapses in AD.[3] However, it is very unlikely that any complement protein will be a marker specific for AD. Finally, because of the blood-brain barrier, it is not clear that there will necessarily be any relationship between brain pathology and blood markers. Perhaps any overlap between brain and blood is simply by chance. A recent paper suggests break-

down of the blood-brain barrier in aging human hippocampus,[4] so it might be possible to find a blood signature for AD brain pathology, but such a signature remains to be found and validated. ■

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ABSTRACT & COMMENTARY

Epidemiology of Neuromyelitis Optica Spectrum Disorders in Two Distinct Populations: Black and White

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Perumal reports she receives grant/research support from Genzyme Corp., and is on the speakers bureau for Biogen Idec, Genzyme Corp., Acorda Therapeutics, and Teva Pharmaceuticals.

SYNOPSIS: Based on an epidemiological study in two ethnically and geographically distinct populations of patients diagnosed with central nervous system inflammatory demyelinating diseases, the authors report a higher prevalence among Afro-Caribbean patients in Martinique in the eastern Caribbean sea vs. a predominantly Caucasian population in Olmstead County in Minnesota. The study demonstrates a propensity for neuromyelitis optica to affect blacks more than Caucasians.

SOURCE: Flanagan EP, Cabre P, Weinshenker BG, et al. Epidemiology of aquaporin-4 autoimmunity and neuromyelitis optica spectrum. *Ann Neurol* 2016;79:775-783.

Neuromyelitis optica (NMO) is an inflammatory disease of the central nervous system that preferentially affects the optic nerves and spinal cord. Classic NMO or Devic's disease is characterized by concurrent episodes of optic neuritis (ON) and transverse myelitis (TM). NMO spectrum disorder (NMOSD) is diagnosed in patients with isolated ON or TM who have the NMO IgG (aquaporin-4) antibody, which is potentially pathogenic and has high specificity for this group of diseases. NMO was accepted as a distinct entity from multiple sclerosis (MS) after the discovery of the aquaporin-4 antibody in 2004. The aquaporin-4 test is > 80% sensitive and > 99% specific for NMOSD. Proper identification of NMOSD is imperative as the disease course and treatment options for this disease are different from that of MS.

A few studies from Europe that have reported the prevalence of NMO/NMOSD describe rates between 0.72-4.4/100,000. Large epidemiologic studies have not been reported from the United States, and though it appears that blacks may have a higher incidence when compared to Caucasians, there have not been large studies examining differences between the ethnicities. Given these limitations, the authors undertook a population-based study of the seroprevalence and seroincidence of aquaporin-4 antibody and NMO/NMOSD among patients with inflammatory demyelinating diseases in Martinique, French West Indies, and Olmstead County, Minnesota, respectively.

In Olmstead County, patients were identified from Rochester Epidemiological Project medical records linkage system, which is a database that includes patients seen by all medical practitioners in Olmstead County. Patients with a diagnosis of inflammatory demyelinating diseases (IDD), including MS, NMO, optic neuritis, transverse myelitis, clinically isolated syndrome, ADEMS, or other IDDs, between January 1, 1985, and Dec. 31, 2011, were included. Identified patients were contacted and invited to participate in the study and provide a blood sample for aquaporin-4 antibody assay between 2007 and 2015. Blood samples were collected from 363 of the 434 (84%) prevalent and 104 of 130 (80%) of incident cases of IDD. In Martinique, an IDD population registry has been maintained from 1992, which captures all cases of IDD from hospital-based and clinic-based neurology services and ophthalmology and rehabilitation services, health insurance data, and MS patient associations. One hundred ninety-three of 237 (81%) prevalent and 111 of 122 (91%) incident cases were included in the study. All blood samples collected as a part of this registry were

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Neurology [ALERT]

Stroke Alert

By Matthew E. Fink, MD

Dual Antiplatelet Therapy Appears More Effective Than Single Therapy

SOURCE: Ge F, Lin H, Liu Y, et al. Duel antiplatelet therapy after stroke or transient ischemic attack – how long to treat? The duration of aspirin plus clopidogrel in stroke or transient ischemic attack: A systematic review and meta-analysis. *Eur J Neurol* 2016;23:1051-1057.

The CHANCE study showed that the combination of aspirin and clopidogrel was superior to aspirin alone for reducing the risk of stroke in the first 90 days after a TIA or minor ischemic stroke (*N Engl J Med* 2013;369:11-19). In its 2014 guidelines, the American Heart Association recommended that the combination of aspirin and clopidogrel can be initiated within 24 hours for a minor ischemic stroke or TIA and continued for 90 days. However, the CHANCE trial was performed in China with a discrete ethnic population, and it was not clear if the optimal duration of treatment should be 90 days or longer. In ischemic heart disease, treatment with dual antiplatelet therapy beyond one year is the standard of care in patients who have coronary stents, and this question has been unanswered in patients with transient ischemic attack or stroke. Therefore, the authors performed a comprehensive literature review and meta-analysis, and identified nine randomized controlled trials that included 21,923 patients. In review of these trials, short-term dual antiplatelet therapy significantly reduced the risk of ischemic stroke recurrence by 41% and major vascular events by 30%, without an increased risk of intracranial hemorrhage. Prolonged treatment beyond 90 days reduced the risk of ischemic stroke recurrence by 12% and major vascular events by 10%. However, the risk of major bleeding and intracranial hemorrhage was increased in those patients treated for a longer term. Therefore, it appears that short-term dual antiplatelet therapy appears to be superior to prolonged treatment. However, this difference in outcome needs to be confirmed by further well-designed randomized clinical trials. ■

Which Patients with TIA Are at High Risk for a Recurrent Cerebral Vascular Events?

SOURCE: Yaghi S, Rostanski SK, Boehme AK, et al. Imaging parameters and recurrent cerebral vascular events in patients with minor stroke or transient ischemic attack. *JAMA Neurol* 2016;73:572-578.

Recurrent cerebral vascular events (RCVEs) are one of the main determinants of outcome in patients after minor strokes and transient ischemic attacks (TIAs). The risk of recurrence is highest within 90 days and is particularly high in the first 48 hours. A number of scoring systems have been developed to attempt a prediction and stratify high-risk from low-risk patients. However, the scores have been limited because they were derived from mostly non-neurologist diagnosed TIA samples and their applicability to patients seen by current neurology stroke teams is questionable. The objective of this study is to determine predictors of early recurrent cerebral vascular events among patients with TIA or minor stroke, defined as an NIHSS of 0 to 3. This retrospective cohort study was conducted at two tertiary care centers, Columbia University in New York, and Tulane University in New Orleans, from 2010 until 2014. All patients were diagnosed with a TIA or minor stroke by a neurologist when they presented to the emergency department. The primary outcome was a recurrent neurological event unexplained by any other medical condition. Of 1,258 total patients, 71 had recurrent events. In a multivariate model of prediction for recurrent infarct, the significance predictors were 1) infarcts on neuroimaging (CT or diffusion-weighted MRI), with an odds ratio of 1.75, and 2) large vessel disease etiology, with an odds ratio of 6.69. When both predictors were present, there was a further increase in the risk of patients to have recurrent cerebral vascular events. When neither predictor was present, the rate of recurring events was extremely low (up to 2%). Patients who had recurrent events were less likely to be discharged to home. ■

Cerebral Microbleeds Are Risk Factor for Symptomatic Intracerebral Hemorrhage in Patients Undergoing IV Thrombolysis

SOURCE: Tsivgoulis G, Zand R, Katsanos AH, et al. Risk of symptomatic intracerebral hemorrhage after intravenous thrombolysis in patients with acute ischemic stroke and high cerebral microbleed burden. A meta-analysis. *JAMA Neurol* 2016;73:675-683.

Cerebral microbleeds (CMBs), as visualized on gradient-echo or susceptibility-weighted MRI, are considered markers of bleeding-prone cerebral microvessels and constitute a significant and independent predictor of future intracerebral hemorrhage. However, the risk of these abnormalities in patients undergoing thrombolysis is uncertain, and observational studies have shown conflicting results. The authors undertook a literature review and meta-analysis to investigate the association of a high cerebral microbleed burden (> 10 CMBs on pre-IV thrombolysis MRI) and the risk of symptomatic intracranial hemorrhage following thrombolysis for acute ischemic stroke. Symptomatic hemorrhage was defined as any intracranial bleed with neurological worsening ≥ 4 points on the NIH stroke scale score. After a comprehensive literature review, nine studies were identified comprising 2,479 patients with acute ischemic stroke. The risk of symptomatic intracranial hemorrhage after thrombolysis was found to be higher in patients who had CMBs compared to patients without CMBs (risk ratio = 2.36). A higher risk for hemorrhage was detected in patients with a high CMB burden (> 10 CMBs) when compared with patients who had 0 to 10 CMBs (risk ratio = 12.10). The presence of cerebral microbleeds and a high CMB burden on pretreatment MRI were independently associated with symptomatic intracranial hemorrhage in patients treated for acute ischemic stroke with thrombolysis. CMB burden should be included as part of the individual risk stratification formula for patients when the decision is being made to administer IV thrombolysis. ■

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sent to the Mayo Clinic for AQP4-IgG assay. The Olmstead population was 82% Caucasian and the Martinique population 90% black.

The overall age- and sex-adjusted prevalence of NMO/NMOSD on Dec 31, 2011, was greater in Martinique (10 of 100,000) than in Olmstead County (3.9 of 100,000; P = 0.01). Correspondingly, the age- and sex-adjusted incidence rate of NMO/NMOSD from 2003-2011 was also higher in Martinique (7.3 of 100,000) than Olmstead County (0.7 of 100,000; $P < 0.001$). The ratio of MS to NMO/NMOSD was lower in Martinique than in Olmstead County (3.5:1 vs. 54:1). Due to the small numbers of Asians and Hispanics in the Olmstead study population, data for these groups are limited. The prevalence in Olmstead County (3.9/100,000) is similar to that reported from a Dutch Caucasian study (4.4/100,000) and higher than studies from the United Kingdom (0.72-1.96/100,000), India (2.6/100,000), and Japan (0.9/100,000). The median age of onset (35-37 years) and the female-to-male ratio (5-9:1) was similar in both Olmstead and Martinique population.

■ COMMENTARY

In this one-of-a-kind epidemiological study of the incidence and prevalence of NMO/NMOSD in two distinct populations — a predominantly black population in Martinique, West Indies, and a predominantly Caucasian population in Olmstead County, Minnesota — the authors report a higher prevalence and incidence in Martinique. The authors also report a higher proportion of NMO/NMOSD among inflammatory demyelinating diseases in this population. This is in accordance with earlier studies which suggested that, in addition to having a higher incidence of NMO/NMOSD among blacks, there might be a relatively lower incidence of MS in this population when compared to Caucasians. This study again highlights the genetic and environmental influences in the manifestations of IDDs and adds valuable data on the epidemiology of NMO/NMOSD. ■

CME QUESTIONS

1. **In the elderly, treatment of glioblastoma should include all of the following *except*:**
   a. biopsy of the tumor for accurate diagnosis.
   b. radiation therapy.
   c. aggressive surgical resection.
   d. chemotherapy.
2. **IgG anti-GQ1b antibodies may be seen in:**
   a. Miller Fisher syndrome.
   b. Bickerstaff brainstem encephalitis.
   c. Guillain-Barré syndrome.
   d. All the above
3. **Which of the following has been associated with an increased risk of mild cognitive impairment or dementia?**
   a. Apolipoprotein E ε4 carrier
   b. Hypertension
   c. Weight loss
   d. All of the above
4. **Blood biomarkers of amyloid deposition in the brain have been reliably identified in proteomic studies.**
   a. True
   b. False
5. **NMO/NMOSD have which of the following features across different ethnic groups?**
   a. Prevalence and incidence of NMO are lower among the black population compared to the white population
   b. Multiple sclerosis is less common in the black population than is NMO/NMOSD
   c. Multiple sclerosis is less common in the white population than is NMO/NMOSD
   d. The incidence of NMO/NMOSD is higher in blacks than in whites
5. **Following acute ischemic stroke, treatment with a single antiplatelet agent is just as efficacious as treatment with dual antiplatelet medications, and carries a lower risk of intracranial hemorrhage.**
   a. True
   b. False
6. **In patients who present with transient ischemic attack or minor stroke, the period of time with the highest risk of recurrence is the first 48 hours following the initial event.**
   a. True
   b. False

[IN FUTURE ISSUES]

Update on Pain Management