AHC Media
A RELIAS LEARNING COMPANY

Vol. 37, Issue 3, November 2017
AHCMedia.com

Neurology
[ALERT®]

Evidence-based summaries of the latest clinical neurology research

ABSTRACT & COMMENTARY

Pitfalls in the Treatment of Seizures Associated With Brain Tumors

By Padmaja Kandula, MD

Assistant Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Cornell Medical College

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

SYNOPSIS: In this multicenter, observational study, the authors assessed the prevalence of neuropsychiatric side effects from medications in subjects with tumor-related epilepsy. Levetiracetam was found to have the highest prevalence of such side effects.

SOURCE: Bedetti C, et al. Neuropsychiatric adverse events of antiepileptic drugs in brain tumour-related epilepsy: An Italian multicentre prospective observational study. *Eur J Neurol* 2017;24:1283-1289.

The treatment of brain tumor-related epilepsy is a challenging paradigm, often requiring a fine balancing act between efficacy and side effect profile. Up to 50% of brain tumor patients may experience a seizure in the course of their disease. Hence, the variables associated with optimal efficacy and minimal adverse effects should dictate early appropriate anticonvulsant drug selection in these patients. This multicenter, prospective, observational study evaluated the tolerability of anticonvulsant use based on tumor localization, tumor subtype, and oncologic treatment.

Researchers recruited 259 patients with brain tumor-related epilepsy from regional health centers across Italy from 2010 to 2014. All patients were older than 18 years of age, had documented epilepsy secondary to either primary or metastatic brain tumor, were on anticonvulsant monotherapy, and had no previous exposure to prior anticonvulsants. Patients on anticonvulsant monotherapy, prior personal or family psychiatric history, inoperable brain tumor, end-stage renal disease, or pregnancy were excluded. All brain tumors were classified according to the 2007 WHO Classification of Tumors. Seizures were classified according to the International League Against Epilepsy Guidelines. Seizure frequency at baseline and at five-month follow-up were recorded. Anticonvulsant efficacy was defined as ≥ 50% reduction in seizure counts from baseline or seizure freedom. Practitioners were allowed to titrate anticonvulsants according to standard clinical practice,

Financial Disclosure: *Neurology Alert*'s editor in chief, Matthew Fink, MD, reports he is a consultant for Procter & Gamble. Peer reviewer M. Flint Beal, MD; executive editor Leslie Coplin; editor Jonathan Springston; and AHC Media editorial group manager Terrey L. Hatcher report no financial relationships relevant to this field of study.

Neurology [ALERT]

Neurology Alert,
ISSN 0741-4234, is published monthly by AHC Media, a Relias Learning company
111 Corning Road, Suite 250
Cary, NC 27518
AHCMedia.com
GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to AHC Media, LLC P.O. Box 74008694, Chicago, IL 60674-8694.

SUBSCRIBER INFORMATION
(800) 688-2421
Customer.Service@AHCMedia.com
AHCMedia.com

Questions & Comments:
Please contact Leslie Coplin, Executive Editor, at lcoplin@reliaslearning.com

Subscription Prices
United States:
Print: 1 year with free *AMA PRA Category 1 Credits™*: $369
Add $19.99 for shipping & handling.
Online only: 1 year (Single user) with ***free*** *AMA PRA Category 1 Credits™*: $319

Multiple Copies: Discounts are available for group subscriptions, multiple copies, site-licenses, or electronic distribution. For pricing information, please contact our Group Account Managers at Groups@AHCMedia.com or (866) 213-0844.

Back issues: Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Canada: Add 7% GST and $30 shipping.
Elsewhere: Add $30 shipping.

ACCREDITATION
Relias Learning is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Relias Learning designates this enduring material for a maximum of 2.25 *AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

This CME activity is intended for the neurologist. It is in effect for 36 months from the date of the publication.

AHC Media
A RELIAS LEARNING COMPANY

with titration periods not exceeding 14 days. The Standardized 12-item Neuropsychiatric Inventory Test was administered to all patients or caregivers at the time of inclusion and at the five-month mark.

Approximately 55% of enrolled patients were male. Median age was 52 years. Glioblastoma was the most common tumor pathology (43%), followed by astrocytoma (17%), oligodendroglioma (15%), meningioma (9.7%), metastasis (7%), oligoastrocytoma (7%), and the remaining patients comprising hemangiopericytoma, craniopharyngioma, and central neurocytoma.

Nearly 50% of tumors were in the frontal lobe. The temporal lobe was the second most common region for tumor localization (21%). The majority of the patients experienced focal seizures with or without impaired awareness (60%). Nearly 58% of patients were prescribed levetiracetam monotherapy, followed by phenobarbital (14.8%), oxcarbazepine (8.5%), and valproate (7%).

All patients had > 50% reduction in seizures from baseline. In addition, nearly 95% of patients had ≥ 75% seizure reduction rate. All patients underwent surgical resection, with 42% undergoing dexamethasone treatment, 48% chemotherapy with temozolomide, 46% radiotherapy, and 33% with combination dexamethasone, temozolomide, and radiation.

A multivariate analysis showed no statistically significant difference in neuropsychiatric prevalence and severity with regard to brain tumor side, age, gender, steroid dose, or chemotherapy or radiation alone or in combination. However, patients with frontal lobe tumors had a higher prevalence and severity of neuropsychiatric effects (odds ratio [OR], 7.73; $P < 0.001$) vs. non-frontal tumors. Among patients treated with levetiracetam, those with frontal lobe tumors again had a higher prevalence (OR, 5.00) and magnitude ($P < 0.01$) of neuropsychiatric side effects. There was no dose correlation between levetiracetam and side effects. Multivariate analysis specifically targeting anticonvulsant use revealed that patients receiving levetiracetam had higher prevalence and magnitude of neuropsychiatric effects, regardless of dose, compared to other anticonvulsants (OR, 7.94; $P < 0.01$). Non-neurobehavioral side effects were more common in first-generation anticonvulsants such as phenytoin, phenobarbital, and valproic acid.

■ COMMENTARY

Because of ease of administration, broad-spectrum coverage, and relative lack of drug interactions, levetiracetam increasingly has been used in the treatment of epilepsy and, specifically, in those with brain tumors. However, despite increasing use there has not been a large-scale effort to study the brain tumor population who may be susceptible to anticonvulsant side effects. These study results are not surprising, since levetiracetam has been implicated in a higher incidence of neuropsychiatric side effects. However, it is intriguing that in patients with brain tumors, specifically frontal lobe brain tumors, this effect was not dose dependent. Bedetti et al also raised the possibility of a synergistic effect of frontal lobe tumor localization and levetiracetam treatment. Patients were excluded based on familial or personal psychiatric history. However, those with pre-existing comorbid psychiatric diagnosis or family history may be even more susceptible to levetiracetam effects. Lastly, the authors hypothesized that SV2A gene expression in tumor tissue may be predictive of levetiracetam treatment response and risk of neuropsychiatric side effects. The authors' proposed future histologic analysis of brain tumor genetic markers may be an important factor for treatment success and serve as a goal in this age of precision medicine. ■

ABSTRACT & COMMENTARY

Exploring Cortical Pathology in Multiple Sclerosis With Routine MRI

By Susan Gauthier, DO, MSW
Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Gauthier reports she receives grant/research support from Genzyme, Mallinckrodt, and Novartis.

SYNOPSIS: In this MRI and histopathological study, the investigators showed that cortical T1w/T2w ratio was unrelated to myelin density, but had a strong correlation with dendritic density. Furthermore, abnormal values within the posterior cingulate cortex correlated with impairment in cognitive domains.

SOURCE: Righart R, et al. Cortical pathology in multiple sclerosis detected by the T1/T2-weighted ratio from routine magnetic resonance imaging. *Ann Neurol* 2017; Aug. 18. doi: 10.1002/ana.25020 [Epub ahead of print].

Multiple sclerosis (MS) is a complicated disease with both inflammatory (relapsing) and degenerative (progressive) stages. Traditionally, studies have focused on pathological changes within the white matter (WM) as the trigger for secondary neuronal loss and sustained clinical progression in MS. However, recent evidence has suggested that primary gray matter (GM) pathology contributes significantly to the progressive process. Cortical demyelination has been appreciated only recently through histopathological studies and in vivo exploration with high-field MRI. MRI studies using magnetization transfer imaging (MTR) and double inversion recovery have revealed that routine clinical MRI sequences are grossly underestimating the lesion load within MS patients. The ability to study cortical pathology with routine clinical MRI could allow for the exploration of cortical pathology among much larger populations and provide a pathway to determine the influence of cortical lesions on the natural course of the disease.

Righart et al used a conventional 3T MRI to obtain three-dimensional (3D) gradient-echo T1weighted (w) and high-resolution T2w sequences to create a cortical map of the T1w/T2w signal. Previous work has suggested that cortical T1w/T2w ratio is reflective of myelin; however, this conclusion was drawn through indirect evidence, and no direct histological comparison has ever been reported. In this study, cortical T1w/T2w ratios from 168 MS patients (either clinically isolated syndrome or relapsing-remitting) were compared to 80 age-matched healthy controls (HC). The T1w/T2w ratio values were sampled at the mid-thickness surface, which is midway between the WM and GM surfaces, using FreeSurfer software, which provides cortical GM surface thickness maps. The investigators compared T1w/T2w ratios within the whole cortex and derived regional differences through voxel-wise general linear models. In addition, researchers collected clinical parameters such as EDSS, MSFC, as well as cognitive testing focused on the core cognitive deficits generally found in MS. Lastly, the study included a postmortem analysis of nine progressive MS patients to provide histopathological validation for cortical T1w/T2w ratio.

The investigators found that the T1w/T2w ratio across the whole cortex was lower in MS compared to HC. Four regional clusters were identified: left and right medial occipital cortex as well as the right and left posterior cingulate cortex. Given the integral role of the posterior cingulate in memory and attention, the T1w/T2w ratio in this region was associated with clinical metrics to provide a functional relevance to the MRI metric. Wordlist retrieval correlated with T1w/T2w ratio within this region after appropriately controlling for multiple comparisons, age, cortical thickness, and WM lesions. In the postmortem analysis, the strongest correlation of cortical T1w/T2w ratio was determined to be with dendrite density ($P = 0.0008$), and no trends were found with myelin density, axonal density, or cortical thickness. The average T1w/T2w ratio within the posterior cingulate cortex was plotted across all populations studied (HC, in vivo imaging, and postmortem) and suggested a declining slope associated with advancing disease stage.

[Recent evidence has suggested that primary gray matter pathology contributes significantly to the progressive process of multiple sclerosis.]

■ COMMENTARY

Cortical T1w/T2w ratio has a strong advantage over high-field imaging, given that these sequences are commonly acquired as routine standard of care. Many investigators in the field have categorized cortical T1w/T2w ratio as a measurement of myelin based on the knowledge that the T1w signal is predominantly dependent on myelin and reported patterns tended to follow classic studies of cortical myelination. Given the ease of obtaining these data and the interpretation that the data reflect myelin, a number of studies are now starting to emerge using this MRI metric.

Righart et al emphasized the importance of proper histopathological validation and demonstrated the failure of using indirect means to interpret the tissue-specificity of MR signal intensity. Interestingly, they highlighted the role of dendritic density in MS, which has been underrecognized as a contributing factor in disease progression. As the authors noted, significant dendritic damage has been reported to be independent of cortical demyelination and, combined with the current observation, raises the question of the role of dendritic damage in MS disease pathogenesis and, importantly, the potential role in cognitive dysfunction. Although cortical T1w/T2w ratio can be derived from routine imaging, significant methodological development is still needed (because of challenges with cortical segmentation), and more data are required to elucidate the influence of change in cortical T1w/T2w on the disease course of MS. ■

ABSTRACT & COMMENTARY

Childhood Head Trauma and Risk of Subsequent Diagnosis of Multiple Sclerosis

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

SYNOPSIS: A large study that reviewed longitudinally collected data from the national Swedish Patient Register found that head trauma in adolescents was associated with an increased risk of subsequent diagnosis of multiple sclerosis.

SOURCE: Montgomery S, et al. Concussion in adolescence and risk of multiple sclerosis. *Ann Neurol* 2017; Sept. 4. doi: 10.1002/ana.25036 [Epub ahead of print].

Multiple sclerosis (MS) is an inflammatory disorder of the central nervous system that is believed to be triggered by yet unknown environmental causes in a genetically susceptible individual. Several environmental factors have been investigated — vitamin D deficiency, infections including Epstein-Barr virus (EBV), cigarette smoking, and trauma, along with others.

Montgomery et al endeavored to systematically analyze longitudinally collected data from the national Swedish registry to look for a possible association between head injury in childhood and adolescence and risk of subsequent MS. This is the largest study yet that examined trauma before the age of 20 years and the risk of MS. All diagnoses of MS recorded in the Swedish patient registry between 1964 and 2012 were identified based on ICD codes. From these patients, those who were diagnosed with MS after the age of 20 years were identified and matched with 10 controls who did not have a diagnosis of MS for age, sex, and region of residence. In identifying those exposed to head trauma, the investigators only used those with a diagnosis of concussion alone. As a control group for trauma exposure, they selected patients with a diagnosis of limb fracture. Trauma exposures were divided further into a childhood group, in which the trauma occurred between birth and 10 years of age, and an adolescent group, in which trauma occurred between 11 and 20 years of age. The researchers included 7,292 MS patients in the study.

This study found that concussion in adolescence (age 11-20 years) was associated with a statistically significant risk of a subsequent diagnosis of MS, and there was a dose-dependent increase in the risk. The adjusted odds ratios (and 95% confidence intervals) were 1.22 (1.05-1.42; $P = 0.008$) for diagnosis of one concussion and 2.33 (1.35-4.02; $P = 0.002$) for diagnosis of two or more concussions. There was no association between limb fracture and subsequent risk of MS. The authors also found no association between childhood (birth to 10 years of age) concussion and risk of MS.

■ COMMENTARY

Why might there be an increased risk of MS associated with head trauma? Several possible mechanisms include: 1) release of myelin-specific antigens secondary to injury and the subsequent expansion of myelin-specific T cells; 2) release of pro-inflammatory cytokines that might be directly toxic to oligodendrocytes; and 3) neuroinflammation that remains sustained long after the injury. There are limitations to this study's conclusions. A diagnosis of concussion could have resulted in increased neuro-vigilance that led to further investigations and an earlier diagnosis of MS, and confounding factors, such as a low level of education or socioeconomic status, which also might be a risk for both MS and trauma. A diagnosis of concussion alone was used in ascertaining a history of head trauma; other forms of head injury were excluded in the analysis. The authors found that although adolescent concussion was associated with an increased risk of MS, earlier childhood exposure was not. This could be a result of the small number of cases of childhood trauma that were included in the study, but it also could mean that time of exposure to trauma, as the immune system undergoes changes through adolescence, might play a more pivotal role in initiation of inflammation that leads to MS. The observation of increased risk of developing MS after trauma during adolescence is similar to observations in other studies investigating the risk of infection in adolescence, like EBV, and the subsequent diagnosis of MS.

Montgomery et al found a statistically significant association between concussion during adolescence and subsequent risk of MS. This association was even stronger when there was a history of multiple concussions. Based on these data, trauma should be considered one of the modifiable risks for MS and this observation warrants further study. The potential risk of MS from concussions, in addition to other detrimental effects of traumatic injury to the brain, should emphasize the importance of protecting the brain from any kind of injury, including sports injuries, and the wearing of protective gear should be mandatory. ■

ABSTRACT & COMMENTARY

Noninvasive Vagus Nerve Stimulation for Indomethacin-Sensitive Headaches

By Louise M. Klebanoff, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

SYNOPSIS: Trigeminal autonomic cephalgias are notoriously difficult to treat and may be responsive to noninvasive vagus nerve stimulation.

SOURCE: Tso AR, et al. Research letter: Noninvasive vagus nerve stimulation for treatment of indomethacin-sensitive headaches. *JAMA Neurol* 2017;74:1266-1267.

Trigeminal autonomic cephalgias (TACs) are primary headache disorders characterized by unilateral pain and associated ipsilateral autonomic symptoms, including ptosis, periorbital edema, conjunctival injection, lacrimation, nasal congestion, and rhinorrhea. TACs include cluster headache, paroxysmal hemicrania (PH), hemicrania continua (HC), and short-lasting unilateral neuralgiform headache attacks with conjunctival injection and tearing. The duration of individual attacks and the number of attacks that occur daily help distinguish these specific syndromes. PH, with attacks lasting two to 30 minutes and occurring several times a day, and HC, with exacerbations of continuous pain lasting hours or days at a time, also are distinguished by their response to indomethacin. Unfortunately, the high doses of indomethacin sometimes required for pain relief often are tolerated poorly because of gastrointestinal side effects.

Transcutaneous stimulation of the vagus nerve with the gammaCore device has been shown to be effective for the acute treatment of episodic cluster headache. The authors postulated that vagus nerve stimulation also could be useful in PH and HC. Through record review, the authors identified 15 patients with HC (9) and PH (6) who used noninvasive vagus nerve stimulation as either primary treatment (10 patients) or adjuvant treatment (five patients) who continued to take oral indomethacin. GammaCore generates a 120-second electrical impulse of adjustable amplitude that stimulates the vagus nerve when held against the neck. Patients were advised to begin with two 120-second impulses applied ipsilateral to the pain twice daily, titrating up as needed and as tolerated. The doses used ranged from two to four doses twice daily to two or three doses three times a day. The duration of use varied from three months to five years.

Among patients with HC, seven (78%) reported reduced pain severity; two reported reduced frequency of exacerbations; and one reported reduced duration of exacerbations. Among patients with PH, four (67%) reported benefit of treatment; one became attack-free; two reported reduced attack frequency; three reported reduced severity; and one reported shorter duration of attacks. Only one patient needed to reduce the dose of the stimulator because of cutaneous irritation.

■ COMMENTARY

This retrospective study of 15 patients with either PH or HC reviewed the potential benefit of noninvasive vagus nerve stimulation for indomethacin-sensitive headaches. Although only one patient became attack-free with treatment, a majority of patients reported benefit in reduction of attack severity, frequency, or duration. Gastrointestinal side effects often limit the usefulness of indomethacin to treat these primary headache syndromes; non-invasive vagus nerve stimulation tends to be well-tolerated, with only one of 15 patients developing cutaneous irritation. As the authors cited, two randomized trials have shown the benefit of vagus nerve stimulation in cluster headache, another type of TAC. This study provides rationale for a prospective, randomized, sham-controlled trial in the use of vagus nerve stimulation in PH and HC. ■

ABSTRACT & COMMENTARY

Diabetes, HbA1c, and Neuropathy

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: The hallmark of neuropathy associated with type 2 diabetes is reduction of sensory nerve action potential amplitude and not a reduction in conduction velocity, supporting the hypothesis that hyperglycemia causes axonal dysfunction and injury.

SOURCE: Peterson M, et al. Association between HbA1c and peripheral neuropathy in a 10-year follow-up study of people with normal glucose tolerance, impaired glucose tolerance and type 2 diabetes. *Diabet Med* 2017; Sept. 20. doi: 10.1111/dme.13514.

What is the relationship between HbA1c and peripheral neuropathy in patients with normal glucose tolerance (NGT), prediabetes or impaired glucose tolerance (IGT), and type 2 diabetes? To answer this question, Peterson et al performed a 10-year follow-up study on 87 of an original 119 patients recruited between 2004-2007 and enrolled in the population-based Västerbotten (Sweden) Intervention Programme. Of the original 119 patients, six died and 26 declined participation. Clinical definitions followed 1999 WHO criteria for glucose intolerance and diabetes: NGT as a fasting and two-hour plasma glucose concentration of < 6.1 mmol/L (110 mg/dL) and < 7.8 mmol/L (140 mg/dL), respectively; IGT as < 7.0 mmol/L (125 mg/dL) and > 7.8 mmol/L (140 mg/dL), respectively; and type 2 diabetes as > 7.0 mmol/L (125 mg/dL) and > 11.1 mmol/L (200 mg/dL), respectively. Evaluations included a social and medical history questionnaire, assessment of exposure to nicotine or other toxins, serum measurements of HbA1c, complete blood counts, C-reactive protein, lipid profile, creatinine, and homocysteine and thyroid-stimulating hormone levels to exclude B12 deficiency and hypothyroidism. All patients underwent standard nerve conduction studies of the right peroneal motor and sural sensory nerves, the latter deemed most appropriate to evaluate sensory nerve function. Statistical analysis was performed using ANOVA for continuous variables, the chi-square test for categorical variables, paired t-tests, Kendall's tau and Pearson's correlation coefficient and regression analyses, with $P < 0.5$ considered significant.

On average, the mean sural sensory amplitude decreased from 10.9 uV to 7.0 uV ($P < 0.001$) among 74 participants who underwent sural nerve study on both occasions, but no statistically significant decrease of conduction velocity was found between the two periods. Sural sensory nerve action potential amplitude decreased by approximately 1% for every 1% increase in HbA1c, whereas no statistically significant association between nerve conduction velocity slowing and HbA1c level increase was appreciated. Sural sensory amplitude decrease, but not nerve conduction velocity slowing, is associated with increasing HbA1c levels, supporting the notion that axonal degeneration, rather than demyelination, is the central feature of type 2 diabetic neuropathy.

■ COMMENTARY

More than 8% of the general population, and 15% in the over 40-year-old age group, has polyneuropathy, with prediabetes and type 2 diabetes being the most common causes in the United States and Europe. At least 50% of all diabetics develop some form of neuropathy during their lifetime, the most common being a distal, stocking-glove, sensory neuropathy. Etiology remains uncertain, with multiple pathways implicated, most notably the polyol pathway, whereby excess glucose is converted to sorbitol, resulting in osmotic imbalance and stress, with compensatory loss of myoinositol, essential for sodium/potassium ATPase function. Hyperglycemia, with its resultant increased glycolysis, promotes neuronal injury by forming uridine 5-diphosphate-N-acetylglucosamine, which binds serine/threonine onto transcription factors, promoting inflammation and nerve injury. Additionally, increased glycolysis results in the accumulation of diacylglycerol, which activates protein kinase C, leading to insulin resistance, vasoconstriction, hypoxia, and nerve damage. Amadori products form when glucose reacts with protein-bound amino groups, producing advanced glycation end products, which cross link essential proteins, resulting in nerve injury. Excess glucose metabolism overproduces electron donors, resulting in a high proton gradient across the inner mitochondrial membrane, overwhelming the antioxidant response with consequent nerve dysfunction. Emerging evidence also suggests that Schwann cells provide needed energy for axonal function, and disruption of the normal bioenergetic cross talk between Schwann cells and axons may underlie diabetic neuropathy.[1] ■

REFERENCE

1. Feldman EL, et al. New horizons in diabetic neuropathy: Mechanisms, bioenergetics, and pain. *Neuron* 2017;93:1296-1313.

STROKE ALERT

Migraine With Aura, Stroke Risk, and Biomarkers

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a consultant for Roche.

SYNOPSIS: A longitudinal cohort study of twins found no increased stroke risk related to migraine overall, but there was a modestly increased risk for stroke related to migraine with aura. Familial factors and vascular biomarkers associated with migraine with aura may explain its correlation with vascular disease.

SOURCES: Lantz M, et al. Migraine and risk of stroke: A national population-based twin study. *Brain* 2017;140:2653-2662.

Tietjen GE, et al. Migraine and vascular disease biomarkers: A population-based case-control study. *Cephalalgia* 2017; Jan 1:333102417698936. doi: 10.1177/0333102417698936 [Epub ahead of print].

A population-based cohort study used data from the Swedish Twin Registry to follow twins without cerebrovascular disease to evaluate migraine as a risk factor for eventual stroke. Twins who were born in the years 1935 to 1958 answered a headache questionnaire during the 1998 to 2002 time period; twins born between 1959 and 1985 answered a headache questionnaire during the 2005 to 2006 time period. Migraine with and without aura and probable migraine were defined according to the International Classification of Headache Disorders criteria. Cerebral ischemia and intracerebral hemorrhage diagnoses were obtained from national patient and cause of death registries. Twins were followed longitudinally, by linkage of national registers, from the date of interview until the date of first stroke, death, or until the study ended late in 2014. In total, 8,635 twins had any migraine/probable migraine headache (3,553 with migraine with aura and 5,082 with non-aura migraine/probable migraine headache) and 44,769 twins had no migraine headache history. Hypertension, peripheral arterial disease, and obesity were more common in non-migraineurs, with atrial fibrillation being less common. During the mean follow-up time of 12 years, there were 1,297 incident (1,073 ischemic and 276 hemorrhagic) strokes, with a mean age at the end of follow-up of 57 years. The data were analyzed using a Cox proportional hazards model, with results finding that any migraine/probable migraine headache and non-aura migraine/probable migraine headache were not associated with an increased risk for stroke. Migraine with aura was associated with a barely significant 27% increased risk for stroke in the initial analysis; but, there were no significant associations between migraine and specific stroke type. The age- and gender-adjusted hazard ratio (HR) for stroke related to migraine with aura was 1.27 (95% confidence interval [CI], 1.00-1.62; $P = 0.05$) and 1.07 (95% CI, 0.91-1.26; $P = 0.39$) related to any migraine/probable migraine headache. The estimated HR for stroke was non-significantly higher in twins younger than 50 years of age and in females. The 2,142 twin pairs discordant for migraine with aura showed an HR for stroke of 1.09 (95% CI, 0.81-1.46), which attenuated the association compared to the primary analysis. Genetic markers for stroke may contribute to this migraine with aura and stroke association.

The association of migraine and vascular disease biomarkers was evaluated in 300 women and 117 men (mean age 48 years) in the CAMERA 1 (Cerebral Abnormalities in Migraine, an Epidemiologic Risk Analysis) substudy of the Dutch general population-based Genetic Epidemiology of Migraine. There were 155 migraineurs with aura, 128 migraineurs without aura, and 134 controls with no severe headaches. The vascular disease biomarkers compared between groups were: fibrinogen, Factor II, D-dimer, high-sensitivity C-reactive protein (hs-CRP), and von Willebrand factor antigen.

DocuSign Envelope ID: 06061AEB-995D-4930-971E-514E2AA73924

Statement of Ownership, Management, and Circulation
UNITED STATES POSTAL SERVICE® **(All Periodicals Publications Except Requester Publications)**

1. Publication Title	2. Publication Number	3. Filing Date
Neurology Alert	0 7 4 1 - 4 2 3 4	10/1/17
4. Issue Frequency	**5. Number of Issues Published Annually**	**6. Annual Subscription Price**
Monthly	12	$369.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4®)*
950 East Paces Ferry Road NE, Ste. 2850, Atlanta
Fulton County, GA 30326-1180
Contact Person: Journey Roberts
Telephone *(Include area code)*: (919) 377-9913

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*
111 Corning Rd, Ste 250, Cary, NC 27518-9238

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*
Publisher *(Name and complete mailing address)*
Relias Learning LLC, 111 Corning Rd, Ste 250, Cary, NC 27518-9238
Editor *(Name and complete mailing address)*
Leslie Coplin, same as publisher
Managing Editor *(Name and complete mailing address)*
Jonathan Springston, same as publisher

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual owner. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
Relias Learning LLC	111 Corning Rd, Ste 250, Cary, NC 27518-9238
Bertelsmann Learning LLC	1745 Broadway, New York, NY 10019

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☑ None

Full Name	Complete Mailing Address

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☑ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, July 2014 *[Page 1 of 4 (see instructions page 4)]* PSN: 7530-01-000-9931 **PRIVACY NOTICE:** See our privacy policy on *www.usps.com*.

DocuSign Envelope ID: 06061AEB-995D-4930-971E-514E2AA73924

13. Publication Title: Neurology Alert
14. Issue Date for Circulation Data Below: September 2017

15. Extent and Nature of Circulation			Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total Number of Copies *(Net press run)*			317	316
b. Paid Circulation *(By Mail and Outside the Mail)*	(1)	Mailed Outside-County Paid Subscriptions Stated on PS Form 3541 (Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)	256	253
	(2)	Mailed In-County Paid Subscriptions Stated on PS Form 3541 *(Include paid distribution above nominal rate, advertiser's proof copies, and exchange copies)*	0	0
	(3)	Paid Distribution Outside the Mails Including Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Paid Distribution Outside USPS®	14	14
	(4)	Paid Distribution by Other Classes of Mail Through the USPS (e.g., First-Class Mail®)	10	8
c. Total Paid Distribution *[Sum of 15b (1), (2), (3), and (4)]* ▶			280	275
d. Free or Nominal Rate Distribution *(By Mail and Outside the Mail)*	(1)	Free or Nominal Rate Outside-County Copies included on PS Form 3541	19	21
	(2)	Free or Nominal Rate In-County Copies Included on PS Form 3541	0	0
	(3)	Free or Nominal Rate Copies Mailed at Other Classes Through the USPS (e.g., First-Class Mail)	0	0
	(4)	Free or Nominal Rate Distribution Outside the Mail *(Carriers or other means)*	5	5
e. Total Free or Nominal Rate Distribution *(Sum of 15d (1), (2), (3) and (4))*			24	26
f. Total Distribution *(Sum of 15c and 15e)* ▶			304	301
g. Copies not Distributed *(See Instructions to Publishers #4 (page #3))* ▶			13	15
h. Total *(Sum of 15f and g)*			317	316
i. Percent Paid *(15c divided by 15f times 100)* ▶			92%	91%

* If you are claiming electronic copies, go to line 16 on page 3. If you are not claiming electronic copies, skip to line 17 on page 3.

DocuSign Envelope ID: 06061AEB-995D-4930-971E-514E2AA73924

Statement of Ownership, Management, and Circulation
UNITED STATES POSTAL SERVICE® **(All Periodicals Publications Except Requester Publications)**

16. Electronic Copy Circulation	Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Paid Electronic Copies ▶		
b. Total Paid Print Copies (Line 15c) + Paid Electronic Copies (Line 16a) ▶		
c. Total Print Distribution (Line 15f) + Paid Electronic Copies (Line 16a) ▶		
d. Percent Paid (Both Print & Electronic Copies) (16b divided by 16c × 100) ▶		

☐ **I certify that 50% of all my distributed copies (electronic and print) are paid above a nominal price.**

17. Publication of Statement of Ownership
☑ If the publication is a general publication, publication of this statement is required. Will be printed in the November 2017 issue of this publication. ☐ Publication not required.

18. Signature and Title of Editor, Publisher, Business Manager, or Owner: Chief Operating Officer — Date: 20-Sep-2017

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including civil penalties).

Stroke-associated clinical phenotypes, including migraine with aura, female sex, and long duration and high attack frequency of aura and of headache, also were evaluated. Fibrinogen and hs-CRP were elevated in migraineurs compared to headache-free controls. Migraine was associated with an increased likelihood of elevated Factor II and hs-CRP. Fibrinogen and Factor II were associated with migraine with aura in women, but not in men. The vascular biomarker hs-CRP was correlated with both increased years and numbers of migraine aura attacks. An increased number of attacks was a significant predictor of elevated von Willebrand factor antigen, D-dimer, and fibrinogen.

■ COMMENTARY

Epidemiological studies have shown that migraine with aura is associated with an increased risk of cerebral and cardiac ischemia. However, an increased cerebrovascular risk has not been shown for individuals with migraine without aura, the predominant migraine subtype. The reason for this consistently demonstrated increase in vascular risk associated with migraine with aura is not clear, with theories including cortical spreading depression, endothelial dysfunction, hypercoagulability, arterial dissection, and embolization through a patent foramen ovale. The Swedish twin study lends credence to a genetic theory linking migraine with aura and ischemic stroke; however, the relatively weak twin correlation indicates a multifactorial association. Given that migraine in general, as well as the specific migraine type, has a very strong familial correlation, a twin association could be expected, even if the migraine type was discordant between twin pairs. Elevated vascular biomarkers were associated with migraine, particularly migraine with aura, as well as with increased years of aura and number of aura attacks. Other studies, including the CAMERA study, have linked increased frequency and duration of migraine auras with neuroimaging findings that have the appearance of white matter ischemic disease.

Elevated vascular biomarkers should be investigated to determine which markers, if any, can be used to stratify risk of vascular events in patients with migraine with aura. All patients at risk of vascular disease should be counseled on the management of the more well-established vascular risk factors. However, migraine with aura in combination with some estrogen-containing contraceptives appears to increase the risk of cerebral ischemia. The ability to counsel women with migraine with aura about contraceptive choices potentially could be enhanced by using biomarker screening to determine the degree of vascular risk. ■

CME QUESTIONS

1. **A statistically significant difference in neuropsychiatric side effect prevalence was noted with which of the following?**
   a. Steroid dose
   b. Dominant hemisphere brain tumors
   c. Combination radiation and chemotherapy
   d. Frontal lobe tumors
   e. Temporal lobe tumors
2. **In patients with multiple sclerosis, T1w/T2w ratio in the cortex demonstrated the highest correlation with which of the following histopathologic features?**
   a. Cortical thickness
   b. Dendritic density
   c. Neuronal density
   d. Axon density
   e. Myelin density
3. **TBI in adolescence might lead to a diagnosis of MS for which of the following reasons?**
   a. Greater neuro-vigilance leads to more imaging, such as MRI.
   b. Subclinical MS might increase an adolescent's risk for sustaining a concussion.
   c. Trauma results in release of myelin-specific antigens.
   d. All of the above
4. **Trigeminal autonomic cephalgias are characterized by all of the following *except*:**
   a. unilateral periorbital pain.
   b. ipsilateral conjunctival injection and/or lacrimation.
   c. ipsilateral nasal congestion and/or rhinorrhea.
   d. third nerve palsy.

[IN FUTURE ISSUES]

Update on Movement Disorders