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INSIDE

Financial Disclosure: *Neurology Alert's* editor in chief, Matthew Fink, MD, is a retained consultant for MAQUET. Peer reviewer M. Flint Beal, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

What Is Our Current Understanding of Epilepsy Prognosis?

ABSTRACT & COMMENTARY

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: *This paper summarizes and focuses on the National General Practice Study of Epilepsy with emphasis on epilepsy prognosis after initial diagnosis.*

Source: Shorvon SD, Goodridge DM. Longitudinal cohort studies of the prognosis of epilepsy: Contribution of the National General Practice Study of Epilepsy and other studies. *Brain* 2013;136(Pt 11):3497-3510.

Our current understanding of epilepsy prognosis stems from the cumulative data of large cohort studies published over the last few decades. In this paper, Shorvon and colleagues review the details of the National General Practice Study of Epilepsy (NGPSE), the first and largest prospective, population-based study of adults and children with epilepsy. The principal endpoint of the study was to describe the prognosis of newly diagnosed seizures with regard to seizure recurrence and remission and mortality. Secondary endpoints included treatment patterns and psychosocial aspects of epilepsy.

Patients for the NGPSE were prospectively recruited through 275 general practitioners (GP) within Great Britain from 1984-1987. At 6-month follow-up, patients were classified into febrile convulsions (220 patients), definite epileptic seizures (564 patients), and possible epileptic seizures (228 patients). Stratification was based on combined clinical information from the referring GP and selected adult and pediatric neurologists with epilepsy training. Of the 564 definite epilepsy cases, 346 were idiopathic/cryptogenic, 119 remote symptomatic, 83 acute symptomatic, and 16 with neurologic deficit. Cerebrovascular disease and stroke were the two most common symptomatic etiologies. Patients were followed at 6 months and subsequently had annual evaluations over a median of 22 years.

VOLUME 32 • NUMBER 4 • DECEMBER 2013 • PAGES 25-32

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Of the 564 patients with definite seizures, 67% and 78% had recurrence at 12 months and 36 months, respectively. Seizures associated with a fixed neurologic deficit from birth had 100% recurrence at 12 months in contrast to 40% recurrence from acute brain insults. In addition, those < 16 years or > 59 years of age also had a high risk of seizure recurrence (83%). Other factors associated with risk of recurrence included partial seizures (94%) vs 72% for generalized seizures. The rate of relapse was inversely related to duration of seizure freedom. The hazard rate for seizure recurrence or percentage risk of having a recurrence was 0.033 per week in the first 6 months after the first seizure, then fell to 0.007 per week at 6-12 months, and finally 0.004 per week in the next 24 months. The overall relapse rate at 3 years after the first seizures was roughly 75%, but 44% if no relapse in the first 6 months, 32% if no relapse after 12 months, and 17% if no relapse at 18 months.

In terms of remission, the number of seizures in the first 6 months after study notification (seizure density) predicted chance of remission. Hence, for an individual with two seizures during the 6-month period, the chance of making the 1-year remission rate was 95% and 47% for 5-year remission vs 75% and 24%, respectively, for individuals with high seizure density (≥ 10 seizures during the 6-month period).

For individuals with febrile convulsions, 6% of the children ultimately developed epilepsy (mean follow-up of 21.6 years). The standardized mortality rate (SMR; ratio quantifying the increase or decrease in mortality of a study cohort with respect to the general population) for patients with possible epilepsy was 2.5 vs 3 for those with definite epilepsy. The SMR was the highest at 5.1 during the initial year of diagnosis, then declined to 2.5 and 1.3 at 3 and 5 years, respectively. The SMR for those with idiopathic epilepsy was 1.6, remote symptomatic epilepsy 4.3, and acute symptomatic epilepsy 2.9. The authors concluded that the mortality rate was higher in those with newly diagnosed epilepsy largely due to underlying cause. Seizure recurrence and antiepileptic drug treatment did not influence mortality rate. At median follow-up of 22.8 years, SMR for those with definite epilepsy was 2.55, with pneumonia and cerebrovascular disease as most common causes of death.

In terms of treatment patterns, nearly 50% of those on treatment were in 5-year remission. Twenty-nine percent of patients with one or more seizures a week had never tried a second agent and only 23% had tried four or more antiepileptic drugs.

Using the Washington psychosocial inventory, a questionnaire was sent to 216 patients with an 89% response rate. The four major problem areas identified by patients were fear of seizures, fear of stigma in employment, adverse effects on leisure, and lack of energy. The conclusion of the questionnaire was that psychosocial impact was related to severity of the illness rather than the diagnosis itself.

■ COMMENTARY

Based on this longitudinal, prospective study, a few generalizations regarding epilepsy prognosis can be made. Overall, epilepsy has a good prognosis, with 65-85% remission rate. In particular, the long-term prognosis for febrile seizures developing into epilepsy in children was 6%. The likelihood of long-term remission is better in newly diagnosed cases rather than chronic cases. Early treatment response to seizures is an indicator of overall long-term prognosis. The longer the overall remission period, the less likelihood of subsequent seizure recurrence. In contrast, the longer the epilepsy is active, the prognosis is poorer. Remission periods followed by relapse were less common than initial active seizures with remission and no remission at all (refractory state). Epilepsy has the highest mortality rate in the initial years after diagnosis and appears to be dependent largely on underlying cause. Lastly, clinical factors predicting worse prognosis are presence of fixed neurologic deficit early in life, high seizure density before treatment, poor initial response to antiepileptic drug treatment, and certain epilepsy syndromes.

Perhaps the most puzzling question is why epilepsy prognosis continues to improve. Although it seems intuitive that the ever-increasing clinical armamentarium of

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media LLC, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball
INTERIM EDITORIAL DIRECTOR: Lee Landenberger

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to *Neurology Alert,* P.O. Box 550669, Atlanta, GA 30355.

Back Issues: $42. Missing issues will be fulfilled by customer service free of charge when contacted within one month of the missing issue's date.

Subscriber Information

Customer Service: 1-800-688-2421.
Customer Service E-Mail: customerservice@ahcmedia.com
Editorial E-Mail: leslie.coplin@ahcmedia.com
Online: www.ahcmedia.com

Subscription Prices

United States
1 year with free AMA Category 1 credits: $319
Add $17.95 for shipping & handling.
(Student/Resident rate: $125)

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Questions & Comments
Please call **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

second- and now third-generation antiepileptic agents may have a large role in the matter, to date there have been no epidemiologic data to firmly support this hypothesis. In the future, an analysis comparing epilepsy prognosis of first- and second-generation medications is warranted to thoroughly answer this clinical question. ■

Sometimes Coma Is Not a Coma

ABSTRACT & COMMENTARY

By Andrew Goldfine, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Novel protocols with functional MRI may allow clinicians to determine if some unresponsive patients are able to hear, understand, and respond to questions.*

Source: Naci L, Owen AM. Making every word count for nonresponsive patients. *JAMA Neurol* 2013 Aug 12; doi:10.1001/jamaneurol.2013.3686 [Epub ahead of print].

VEGETATIVE STATE (VS) AND MINIMALLY CONSCIOUS STATE (MCS) are behaviorally defined as no interaction and minimal interaction with the environment, respectively. Of increasing concern is that patients with these syndromes may be misdiagnosed and actually have higher levels of consciousness than they demonstrate on exam, due possibly to fluctuating level of arousal or disproportionate damage to motor systems. Proper diagnosis is essential, as patients in MCS have a higher likelihood of recovery to independence than those in VS, and patients with full consciousness theoretically could communicate through brain-computer interfaces.

To bypass damaged motor systems, investigators have recently made use of brain imaging tools including functional magnetic resonance imaging (fMRI) and electroencephalography (EEG), with the typical output being change in brain activity to a command. In *JAMA Neurology*, Naci and Owen report taking this approach one step further by developing a fMRI system to allow patients to communicate. This same research group previously reported a case of a VS subject who communicated through fMRI (imagine playing tennis for yes and navigating around your house for no), but here they report on an experimental paradigm that is more natural for a patient to perform.

In this study, subjects had fMRI performed while they listened to a voice say the words "yes" or "no" in alternate blocks of 22 seconds. These target words were interspersed with the numbers one through nine as distractors. At the beginning of each block, subjects were asked a question (e.g., "Is your name Steven?") and then told to attend to the word that answered the question.

To analyze the data, the authors compared brain activity during "yes" and "no" blocks. To narrow down where to look for a response, they first exposed the subjects to the same stimuli, but instead asked them to count the target words (yes/no) or just relax. The comparison of "count" to "relax" blocks revealed brain regions involved in attention, which were then used in the communication runs as "regions of interest" for analysis. This process allowed the authors to have subject-specific brain regions of interest, essential as these subjects had widespread brain injury and years of potential plasticity for recovery.

The authors report on one MCS and one VS subject who demonstrated evidence of communication — increased activation of attention-related brain regions during presentations of the correct answer (yes/no). In the MCS subject, the results were positive two out of four times, while in the VS subject results were positive four out of four times (two at one visit and two 5 months later). They do not report on other subjects they tested who may have had negative results.

■ COMMENTARY

This study offers a novel approach for detection of consciousness with some advantages and disadvantages to other approaches. Compared to the more standard task of motor imagery (e.g., playing tennis), this approach is more natural (attend to the word yes for a yes response) and does not require an intact motor imagery network (though like all existing approaches, does require language, thereby excluding subjects with aphasia). Their approach also has the advantage of subject-specific regions of interest, rather than requiring activation in brain regions developed from studies of healthy subjects. The primary disadvantage of this technique is that it uses fMRI, which is an inconvenient means of communicating with a potentially locked-in subject (though a positive result could justify further study with a bedside technology such as EEG).

The clinical implications of this and related studies are still not clear. This study and all others use convenience samples (highly chosen subjects), but to determine the prevalence of patients with positive responses as well as the prognostic significance, we need large-scale studies with randomly chosen subjects. Larger studies are also needed to know who is most likely to have a positive response, e.g., based on type of injury, clinical EEG,

By Matthew E. Fink, MD, *Professor and Chairman, Department of Neurology, Weill Cornell Medical College, and Neurologist-in-Chief, New York Presbyterian Hospital*

Nontraumatic Subarachnoid Hemorrhage with Vasoconstriction Should be Differentiated from Aneurysmal Subarachnoid Hemorrhage

Source: Muehlschlegel S, et al. Differentiating reversible cerebral vasoconstriction syndrome with subarachnoid hemorrhage from other causes of subarachnoid hemorrhage. *JAMA Neurol* 2013 Aug 12; doi: 10.1001/jamaneurol.2013.3484. [Epub ahead of print].

Reversible vasoconstriction syndrome (RVCS) is a poorly understood cause of spontaneous subarachnoid hemorrhage (SAH) that may present with sudden thunderclap headache, SAH, intracerebral hemorrhage, or ischemic stroke, and shows angiographic evidence of multifocal and bilateral arterial constrictions. An intensive search for ruptured aneurysm (aSAH) is often ensued, and the end result may be that many useless and potentially morbid tests are performed. Additionally, therapies for aSAH may be instituted that have adverse effects and are not indicated.

The authors reviewed all of their cases of non-aneurysmal SAH at their two hospitals (Massachusetts General and University of Massachusetts Medical Center) and identified important clinical and imaging differences between a group of patients with RVCS (n = 38), a group with aSAH (n = 515), and a group with cryptogenic subarachnoid hemorrhage (cSAH; n = 93).

Predictors differentiating RCVS from aSAH included younger age, chronic headache disorder, prior depression, prior chronic obstructive pulmonary disease, lower Hunt-Hess Grade, lower Fisher CT score, higher number of affected arteries, and bilateral arterial constriction. Predictors that differentiated RCVS from cSAH were younger age, female sex, prior hypertension, chronic headache disorder, lower Hunt-Hess grade, lower Fisher CT score, and the presence of bilateral narrowing. The underlying common denominator for the development of RVCS may be serotonin excess, since many of the patients were exposed to the SSRI-class of medications. In most cases, patients with RVCS can de differentiated from aSAH and cSAH using clinical and imaging features. ■

or imaging findings. Without this guidance, widespread implementation of these techniques may result in many false-positive or inconclusive results that could misguide therapeutic interventions. ■

Does Dietary Nicotine Protect Against Parkinson's Disease?

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

Dr. Henchcliffe reports she is on the speakers bureau and advisory board for Allergan and Teva; speakers bureau for Boehringer-Ingelheim, GlaxoSmithKline, and Novartis; advisory board for Merz; and is a consultant for Gerson Lehman Group and Guidepoint Global.

Synopsis: *This population-based, case-control study suggests that dietary intake of peppers and related species may be associated with decreased risk of Parkinson's disease. These plants are related to tobacco, raising the possibility that nicotine may be the underlying link.*

Source: Searles Nielsen S, et al. 2013 nicotine from edible *Solanaceae* and risk of Parkinson disease. *Ann Neurol* 2013;74:472-477.

This case-control study evaluated risk of Parkinson's disease (PD) associated with dietary nicotine intake from edible plants of the *Solanaceae* family. A total of 490 newly diagnosed PD cases were compared with 644 controls. Of these participants, 63% of cases and 64% of controls were men, and mean age at the time of assessment was 66 years old (cases) and 68 years old (controls). Half of the PD cases and 62% of controls were classified as having significant history of smoking. PD cases were diagnosed by a movement disorders expert or by chart review by a team of neurologists at two centers in the Pacific Northwest. Edible *Solanaceae* family members studied were peppers, tomatoes including tomato juice, and potatoes (baked or mashed only), and nicotine intake associated with these was estimated based upon standard values for dry weight. A number of other non-*Solanaceae* vegetables also were evaluated. Logistic regression was used to calculate odds ratios with adjustments made for age, sex, race/ethnicity, non-*Solanaceae* vegetable intake, to-

Ischemic Stroke in Young Adults Is Associated with a Different Frequency of Risk Factors than in the Older Patient Population

Source: Barlas NY, et. al. Etiology of first-ever ischaemic stroke in European young adults: The 15 cities young stroke study. *Eur J Neurol* 2013;20:1431-1439.

Fifteen European stroke centers combined their data regarding the first-ever ischemic stroke in 1331 patients aged 15-49, to investigate the etiology of their stroke, based on age and gender differences. Classification was done according to Trial of Org in Acute Stroke Treatment (TOAST) criteria: large-artery atherosclerosis (LAA), cardioembolism (CE), small-vessel occlusion (SVO), other determined etiology, or undetermined etiology. CE was categorized into low- and high-risk sources. "Other determined" group was divided into dissection and other non-dissection causes. Comparisons were done using logistic regression, adjusting for age, gender, and center heterogeneity.

Of note, etiology remained undetermined in 39.6%, which is higher than in other published series. Other determined etiology was found in 21.6%, CE in 17.3%, SVO in 12.2%, and LAA in 9.3%. Other determined etiology was more common in females and younger patients, with cervical artery dissection being the single most common etiology (12.8%). CE was more common in younger patients. Within CE, the most frequent high-risk sources were atrial fibrillation/flutter (15.1%) and cardiomyopathy (11.5%). LAA, high-risk sources of CE, and SVO were more common in males. LAA and SVO showed an increasing frequency with age.

Although it is impossible to determine this with certainty, it is presumed that many of the "undetermined" cases were caused by cardiogenic embolism, but this was never ascertained. We know that the longer one does remote cardiac rhythm monitoring, the more likely it is to pick up intermittent atrial fibrillation, and this may be part of the explanation. In any case, CE and arterial dissection are common causes of ischemic stroke in young adults and should be looked for intensively. ■

bacco, and caffeine. Other potential confounders excluded were education, family history of PD, estimated alternative Mediterranean diet score, body mass index, and secondary smoking. The odds ratio (OR) for Parkinson's disease related to *Solanaceae* intake was 0.81 (95% confidence interval [CI], 0.65-1.01; *P*-trend = 0.07). However, by breaking down into different *Solanaceae* family members, this value was driven by intake of peppers (OR, 0.43; 95% CI, 0.24-0.78; *P*-trend = 0.005). For tomatoes, the OR was 0.83 (95% CI, 0.56-1.24) and for potatoes was 1.12 (95% CI, 0.73-1.7). Nicotine from eggplant intake was insufficient to meet the limit of quantitation. Not only were peppers associated with a lower risk of Parkinson's disease, an inverse association of PD risk with increasing pepper consumption was identified. For all participants, eating peppers 2-4 times weekly was associated with an OR of 0.7 (95% CI, 0.50-1.00), whereas the OR for daily intake was 0.5 (95% CI, 0.22-1.15). This inverse association was more pronounced in those who were not tobacco users.

■ COMMENTARY

Tobacco smoking has been associated with decreased Parkinson's disease (PD) risk in multiple studies, and nicotine has been suggested as the tobacco component responsible. This study addresses whether dietary intake of nicotine may have a similar association, and provides support for a link between risk of PD and dietary intake of edible plants of the *Solanaceae* family, which include peppers, tomatoes, potatoes, and eggplants, as well as tobacco. Not only does the study supports an association with dietary nicotine intake, but also a potential dose response, since the greatest risk reduction was associated pepper intake (highest nicotine content per kilogram of all the vegetables assessed here). Additionally results were more compelling in the subgroup of subjects who were not tobacco users vs those who were. All of this, therefore, supports a role for nicotine as at least one of the chemical compounds responsible for the inverse association of *Solanaceae* ingestion with PD risk. Moreover, nicotine possesses neuroprotective properties in the rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine animal models of PD. However, caution should be used in interpreting these results. Dietary data collection relies on subject self-report. Certain foodstuffs were not included, for example salsa or French fries. There is also first-pass metabolism in the liver that cannot be accounted for in such a study design. It is always challenging to discern which of an array of chemical constituents is/are relevant to risk modification. Peppers, in addition to containing nicotine, are excellent sources of nutrients previously found to be associated with lower

PD risk, such as carotenoids, and also provide multiples of the B vitamins and trace elements. Nonetheless, this study now provides independent support for a potential role of nicotine as neuroprotectant, and should stimulate further study as a potentially modifiable risk factor. It is, therefore, timely that an international clinical trial is now underway to examine the effect of transdermal nicotine administered in early PD. ■

MR-Perfusion Patterns of Progressive Multifocal Leukoencephalopathy Lesions Affect the Risk of Developing IRIS

ABSTRACT & COMMENTARY

By Joseph Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Hyperperfusion of progressive leukoencephalopathy lesions (PML) on MRI predicts progression of PML and reduced risk of immune reconstitution inflammatory syndrome.*

Source: Khoury MN, et al. Hyperperfusion in progressive multifocal leukoencephalopathy is associated with disease progression and absence of immune reconstitution inflammatory syndrome. *Brain* 2013;136:3441-3450.

Progressive multifocal leukoencephalopathy (PML) is a central nervous system opportunistic infection caused by the JC virus. Originally described in patients with hematologic malignancies, it became quite common in the height of the AIDS era and over the past few years has been noted in the setting of immunomodulatory therapy for multiple sclerosis (MS) and a variety of other autoimmune disorders. The prognosis of patients with PML has traditionally been quite poor, but with the advent of highly active antiretroviral therapy (HAART), it has improved. However, reconstitution of the immune system, either with HAART in HIV patients or after withdrawal of the offending immunomodulatory therapy in patients with MS, can lead to immune reconstitution inflammatory syndrome (IRIS). PML-IRIS can cause worsening of neurological symptoms and imaging findings and can lead to permanent neurologic dysfunction if not identified and treated rapidly.

In this study, the authors studied the predictive value of the presence of hyperperfusion in PML lesions on the risk of progression and IRIS. MR-perfusion using arterial spin labeling does not require the administration of IV contrast and was used in this study to determine perfusion in PML lesions. The authors had initially hypothesized that hyperperfusion in PML lesions would be associated with increased immune activation and affect risk of IRIS. The study was designed as an observational study. Patients were divided retrospectively into survivors or progressors depending if they lived more than or less than 1 year from the onset of neurological symptoms. A total of 22 patients were enrolled. Eleven were survivors and 11 were progressors. The only statistically significant demographic difference between the groups was age, with median age 19 years older in the progressors than the survivors. Although HIV patients accounted for 64% of the survivors and 27% of the progressors, this was not a statistically significant difference. Initial Karnofsky score and modified Rankin scale score tended to be better in the patients who were ultimately survivors.

Hyperperfusion in PML lesions on MRI was found to be associated with a higher risk of progression and a lower risk of IRIS. In fact, only one PML survivor demonstrated hyperperfusion. The authors calculated a 9.1 relative risk of PML progression with hyperperfusion as measured by MRI. The presence of hyperperfusion in PML lesions was found to have sensitivity of 81.8% and specificity of 90.9% to predict progression. Additionally, the results suggested that hyperperfusion was also associated with reduced risk of developing IRIS. The mean perfusion was much lower in patients who developed IRIS compared to those who didn't. The predictive value was quite good, with 90% of patients with hyperperfusion not developing IRIS. Additionally, hyperperfusion was not associated with contrast enhancement on MRI.

■ COMMENTARY

This study concludes that MR perfusion can risk-stratify patients with PML, with hyperperfusion associated with a higher risk of progression and a lower risk of IRIS. If validated, this would be a very useful predictive tool in clinical practice as it is noninvasive, does not require administration of IV contrast, and can be done at the same time patients obtain other standard MRI sequences. It is interesting that hyperperfusion is not associated with IRIS, as one might predict. Instead, the authors suppose that hyperperfusion may be directly related to viral activity. How can we apply these findings to neurologic practice? In patients with PML, we might order MR perfusion images and in patients who have hyperperfusion perhaps worry less that they will develop IRIS, but worry more about their overall prognosis. ■

Expanding the Myasthenic Phenotype

ABSTRACT & COMMENTARY

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: *A rare form of myasthenia gravis with antibodies to clustered acetylcholine receptor has similar clinical features as the common form with nicotinic receptor antibodies.*

Source: Devic P, et al. Antibodies to clustered acetylcholine receptor: Expanding the phenotype. *Eur J Neurol* 2013 Sep 21; doi: 10.1111/ene.12270. [Epub ahead of print].

Approximately 6-12% of myasthenia gravis (MG) patients are seronegative for antibodies to the nicotinic acetylcholine receptor (AchR), muscle specific kinase (MuSK), and lipoprotein receptor-related protein 4 (LRP4). Some of these seronegative patients have antibodies that bind high-density AchR clusters. How common are such patients in the MG population and how do these patients compare clinically to those with seropositive MG?

Through a nationwide, multicenter, collaboration of French neurologists, 37 seronegative MG patients were collected and included in this study. Inclusion criteria required a clinical picture of generalized MG, response to standard medication including cholinesterase inhibitors and immunosuppression, a > 10% decremental response on repetitive nerve stimulation, and absence of AchR and MuSK antibodies based on radio-immunoprecipitation assays. All 37 sera then underwent immunofluorescence analysis to detect antibodies to clustered AchR.

Among the 37 seronegative patients' sera, those of four men and two women (16%), with a mean age of 45 years and mean disease duration of 11 years, contained antibodies to AchR only when clustered. Symptoms in these six patients resembled those of seropositive MG patients, including fluctuating ptosis, ophthalmoparesis, and limb weakness responsive to cholinesterase inhibitors, with three demonstrating bulbar involvement that was never predominant and all responding well to intravenous immunoglobulin. Early-onset disease, before 40 years of age, was seen in three, all of whom responded well to immunosuppression, with two undergoing thymectomy, one for thymoma, and the other showing thymic hyperplasia histologically. Only one older onset patient remained refractory to standard immunosuppression, including steroids, plasma exchange, and cyclophosphamide, ultimately responding well to rituximab. MG patients positive for antibodies to clustered AchR resemble those with the more common nicotinic AchR autoantibody.

■ COMMENTARY

Among patients with generalized MG, approximately 80-85% have autoantibodies to muscle AchR and another 5% to MuSK. In 2011, three groups separately identified autoantibodies to low-density LRP4 in MG patients previously double seronegative. Enzyme-linked immunosorbent assay and the more sensitive radio-immunoprecipitation assay (RIPA) traditionally have been used to detect these autoantibodies but newer methods, not generally available, have shown that seronegative patients often have low levels of these same, as well as other low-affinity, antibodies. One such assay is the so-dubbed "two-step RIPA," which uses much larger volumes of serum than the traditional 5 ul, increasing the sensitivity of the assay. Cell-based assays (CBA), using cell lines expressing the autoantigen, can detect autoantibodies missed by RIPA, and have been used to document AchR antibodies in up to 50% of previously seronegative patients with ocular MG. CBA have also documented MuSK antibodies in patients with ocular MG in whom MuSK antibodies were previously described as rare. Other assays being tested include Luciferase immunoprecipitation systems (LIPS), which

uses recombinant antigens fused to the enzyme reporter Renilla luciferase (Ruc) to detect patient antibodies, and fluorescence immunoprecipitation assays, which operate similar to LIPS but use AchR subunits fused to fluorescent proteins such as green fluorescence protein. Sensitive assays to further define the "seronegative" MG population are anxiously awaited. ■

CME Objectives

Upon completion of this educational activity, participants should be able to:

- discuss current scientific data regarding the diagnosis and treatment of neurological disease;
- discuss the pathogenesis and treatment of pain;
- describe the basic science of brain function;
- discuss new information regarding new drugs for commonly diagnosed neurological conditions and new uses for traditional drugs;
- identify nonclinical issues of importance for the neurologist.

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

1. Which of the following is *NOT* true regarding the prognosis of epilepsy?
a. Epilepsy associated with a neurological deficit at birth has a poor prognosis for cessation of seizures.
b. The longer a person is seizure-free, the greater the likelihood that the person will remain seizure-free.
c. Only 6% of children with febrile seizures will develop epilepsy.
d. In general, epilepsy gets worse with the passage of time.

2. Vegetative state and minimally conscious state are diagnoses based on a clinical neurological examination, and may require revision based on functional MRI findings.
a. True
b. False

3. Which of the following statements regarding nicotine is *NOT* true?
a. Nicotine in cigarette smoke is thought to reduce the risk of developing Parkinson's disease.
b. Edible plants of the *Solanaceae* family, which include peppers, tomatoes, potatoes, and eggplants, contain variable amounts of nicotine.
c. Nicotine appears to have neuroprotective effects.
d. All of the above are true

4. Which of the following is *NOT* true regarding progressive leukoencephalopathy lesions (PML)?
a. PML is caused by the JC virus in immunocompromised patients.
b. Highly active antiretroviral therapy in patients with HIV-associated PML improves survival.
c. The immune reconstitution inflammatory syndrome is benign and does not cause any neurological worsening.
d. Hyperperfusion in PML lesions may predict progression of the disease.

5. Myasthenia gravis patients with antibodies to clustered acetylcholine receptor may demonstrate:
a. fluctuating ptosis.
b. ophthalmoparesis.
c. limb weakness responsive to cholinesterase inhibitors.
d. good response to intravenous immunoglobulin.
e. All of the above

6. The characteristics of Reversible Cerebral Vasoconstriction Syndrome do *NOT* include:
a. thunderclap headache.
b. subarachnoid hemorrhage.
c. ischemic stroke.
d. intracerebral hemorrhage.
e. normal cerebral angiography.

7. Ischemic stroke in young adults most commonly is *NOT* associated with:
a. cardiogenic embolism.
b. atrial fibrillation.
c. large vessel atherosclerosis.
d. arterial dissections.

In Future Issues: **The Link Between Glaucoma and Alzheimer's Disease**

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Volume 31, Numbers 5-12, Pages 33-96
Volume 32, Numbers 1-4, Pages 1-32
January–December 2013

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By Louis Kuritzky, MD

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Volume 18, Number 12 Pages 23-24 December 2013

Goldilocks Unable to Find Amount of Antioxidants That's Just Right

Source: Bjelakovic G, et al. *JAMA* 2013; 310:1178-1179.

The observation that excess oxidative stress is associated with diverse pathologic consequence has been consistently coupled with the obvious next intellectual step: antioxidants *should* be beneficial to prevent these consequences. Unfortunately, no Goldiloks has stepped forward to inform us which antioxidant is too much, which is too little, and which is just right. Or maybe the antioxidant hypothesis is just a fairy tale, after all?

This is not the first time that observational hypotheses have disappointed. In two clinical trials of antioxidant supplementation in persons at risk for lung cancer (combined n > 45,000), the first trial found an *increase* in lung cancer and mortality, and the follow-up trial was discontinued almost 2 years early because of similar outcomes.

This most recent Cochrane systematic review included 78 trials (n = 296,707) performed in both primary and secondary prevention modes. The "bottom line" is worth quoting: "Antioxidant supplements are not associated with lower all-cause mortality. Beta carotene, vitamin E, and higher doses of vitamin A may be associated with *higher* all-cause mortality." Some naysayers would suggest that we have not yet fulfilled the Goldilocks systematic approach: Maybe we used too little, maybe we used too much, or maybe we used the wrong formation, and have not yet found the approach that's "just right." For now, the science does not support a role for antioxidants in primary or secondary prevention. ■

Antipsychotics Are Associated with Increased VTE Risk

Source: Wu CS, et al. *J Clin Psychiatry* 2013;74:918-924.

Antipsychotics have suffered a beleaguered course of late: literature showing little efficacy advantage of newer vs older agents, concerns about increased mortality associated with their use, etc. A recent report suggests that antipsychotic treatment is also associated with a clinically meaningful increase in risk for venous thromboembolism (VTE), comprised of deep vein thrombosis plus pulmonary embolism.

Wu et al performed a case-control study of enrollees in the National Health Insurance Research Database of Taiwan to compare cases of confirmed VTE (n = 2162) with age-matched controls without VTE (n = 12,966). Initial analysis looked simply at the relative risk of antipsychotic use in persons with VTE vs controls. Second-step analysis adjusted for confounders.

Overall, the adjusted odds ratio for VTE in current antipsychotic users was 1.52 (i.e., current users were 52% more likely to experience VTE than controls); the odds ratio was substantially worse (3.26: a more than 3-fold increase in risk) for new users. These concerning results were attained even after correction for confounding factors such as utilization of thrombogenic medications (e.g., oral contraceptives) and medical comorbidities associated with increased VTE risk (e.g., congestive heart failure). Analysis of different classes of antipsychotics did not find any particular distinction among them. The mechanism by which antipsychotics might increase VTE risk is uncertain, although the authors posit that antipsychotic-induced sedation could lead to less physical activity with subsequent venous stasis. In any case, these data suggest vigilance for VTE in persons prescribed antipsychotics, especially in the early months of use. ■

Physician Visits for Itching

Source: Shive M, et al. *J Am Acad Dermatol* 2013;69:550-556.

If results from the National Ambulatory Medical Care Survey conducted by the CDC are correct, pruritus as a presenting complaint in ambulatory care may merit more of our attention. In a retrospective review of data from 1999-2009, there were approximately 7 million office visits per year in which pruritus (or itching) was indicated as a presenting symptom. In comparison, there were almost 18 million visits per year for low back pain. Since itch may or may not have been specifically indicated when syndromes such as a drug allergic reaction occur, the authors suggest that these numbers likely *underestimate* the true prevalence of pruritus.

The consequences of pruritus may range from minor nuisance to intolerable. Indeed, patients taking opioid analgesia frequently mention pruritus as a treatment-limiting adverse effect. Fortunately, clinicians have a diversity of agents to treat pruritus, including multiple generations of antihistamines as well as steroids (topical and systemic). Finally, it has been

recognized for more than 2 decades that doxepin — traditionally used as an antidepressant — has antihistaminic potency as much as 50 times greater than the most potent "traditional" antihistamines such as hydroxyzine. Because of this antihistaminic potency, doxepin is often used in refractory urticaria, when other antihistamines have failed, even though sedation is common at typical therapeutic doses. ■

Consequences of Non-Adherence in Treated Hypertensives

Source: Cummings DM, et al. *J Am Soc Hypertens* 2013;7:363-369.

The relationship between elevated blood pressure (BP) and stroke is linear and continuous. An abundance of clinical trial data indicate that treatment of hypertension (HTN) by means of numerous diverse classes of antihypertensives lowers stroke risk by ≥ 40%. Clinical trials, however, are not "real life." The Reasons for Geographic and Racial Disparities in Stroke (REGARDS) study is examining a large population (n = 30,239) of southeastern men and women with HTN. Their assessment of the relationship between self-reported degree of antihypertensive medication adherence and serious outcomes (stroke/TIA) from a subset population (n = 15,071) is quite sobering.

During a 5-year window of observation, study participants were grouped into four categories of adherence using the Morisky scale, which translates into general groupings of high, good, moderate, and low adherence. Perhaps not surprisingly, mean systolic BP in the high adherence group was substantially better than the low adherence group (131 mmHg vs 138 mmHg). Incidence of stroke or TIA was 8% higher in the lowest adherence group compared to the highest. Good BP control has meaningful payoff; every decrement of adherence less than that is costly. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media, LLC.
Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media, One Atlanta Plaza, 950 East Paces Ferry Road NE, Suite 2850, Atlanta, GA 30326.

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Long-Term Risk-Reduction Benefits of Sigmoidoscopy and Colonoscopy

Source: Nishihara R, et al. *N Engl J Med* 2013;369:1095-1105.

Participants from two large observational studies provide an opportunity to evaluate the risk reduction accrued from either colonoscopy (COL) or sigmoidoscopy (SIG). The Nurses' Health Study (n = 121,700 female nurses) and the Health Professionals Follow-up Study (n = 51,529 male health professionals) have more than 20 years' prospective follow-up of their participants. During this interval, there were 1185 cases of colon cancer and 474 deaths from colon cancer.

Skeptics have long held fast to the tenet that SIG had an advantage over COL: proven risk reduction for colon cancer mortality for the former. Although the intuitive additional advantage of examining the entire colon with COL seemed a no-brainer, purists argued that whether COL was truly better than SIG was not yet proven, and that since COL was associated with greater risks (perforation, adverse effects from sedation, etc.), there was reasonable basis to continue with SIG as a preferred method. In accord with this philosophy, noting the many missed opportunities for colon cancer screening and prevention, advocacy groups rallied around the call-to-action, "The best colon cancer screening test is whichever one you can get done!"

These data may change that perspective, since the risk reduction for colon cancer death was almost twice as great for COL as SIG (hazard ratios, 0.59 vs 0.32). The "no-brainer" part of the equation was also resoundingly confirmed: COL reduced mortality from proximal colon cancer by more than half compared to no risk reduction through SIG. ■

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Warfarin Outperforms Dabigatran in Patients with Mechanical Heart Valves

Source: Eikelboom JW, et al. *N Engl J Med* 2013;369:1206-1214.

The atrial fibrillation (AF) headlines have been filled with celebration over the efficacy of factor Xa inhibitors (e.g., rivaroxaban, apixaban) and direct thrombin inhibitors (e.g., dabigatran) for prevention of thrombotic events. Since warfarin — though highly effective, exhaustively studied, and time-tested — also has distinct clinical burdens (e.g., need for monitoring, food interactions, drug interactions), agents that were at least as efficacious for thrombotic risk reduction — with fewer of these same clinical burdens — were welcomed.

Success in AF, however, does not necessarily translate into other pathologies. Eikelboom et al studied patients with recent mitral or aortic mechanical valve replacement (n = 252). Subjects were randomized to dabigatran or warfarin. About one-fourth of these patients also had AF.

The trial had to be discontinued early because of untoward events in the dabigatran group: stroke occurred in 5% of the dabigatran group vs none in the warfarin group, and major bleeding was twice as common on dabigatran (4% vs 2%). Although earlier trials in animals were encouraging, these data indicate that warfarin is safer and better tolerated in patients with recent surgery for prosthetic mechanical heart valves. ■

PHARMACOLOGY WATCH

Evidence-based updates in clinical pharmacology

Reglan Safe in Pregnant Women for Nausea and Vomiting

In this issue: Reglan safe in pregnancy; battle brewing over naming of biosimilar drugs; and FDA actions.

Reglan safe in pregnancy

Use of the anti-nausea medication metoclopramide (Reglan) in pregnancy is not associated with an increased risk of major congenital malformations, spontaneous abortion, or stillbirth. These were the findings of large, register-based cohort study from Denmark. The safety of metoclopramide in pregnancy has been of concern because it is increasingly used to treat pregnant women with nausea and vomiting. Metoclopramide-exposed pregnant women were matched with unexposed women in a 1:4 ratio, with more than 40,000 exposed women in the cohort, of whom more than 28,000 received the drug in the first trimester. The drug was not associated with major malformations or any of more than 20 individual malformations. There was no increase in spontaneous abortion, stillbirth, preterm birth, low birth weight, or fetal growth restriction (*JAMA* 2013; 310:1601-1611). ■

Battle over naming of biosimilar drugs

A battle is shaping up between biotech companies and the Generic Pharmaceutical Association (GPhA) over the naming of biosimilar drugs. Biosimilars, or "follow-on biologics," are products whose active ingredient is an approved version of a previously approved biopharmaceutical. Since biologics are generally manufactured in a complex process that may include molecular clones and proprietary cell lines, it is virtually impossible for the manufacturers of a biosimilar to match the process step-by-step. This results in small differences between the innovator product and the follow-on product (hence the name "biosimilar"). With billions of dollars of revenue at stake, biotech companies, such as Genentech and Amgen, have been lobbying federal and state legislators to tighten the rules regarding use of biosimilars. There has also been concern that the FDA might prohibit biosimilar manufacturers from using the same generic name as the original drug, a move that biotech companies would endorse and the GPhA would strongly oppose. A bipartisan group of senators recently entered the fray by penning a letter to the FDA urging the agency to allow biosimilars to share the name of the innovator product. Led by Republican John McCain and Democrats John Rockefeller and Tom Harkin, six senators urged the FDA to follow the intent of the Biologic Price Competition and Innovation Act, suggesting that if biosimilars were not allowed to share the same name it would undermine "the safety and accessibility of affordable biosimilars." The FDA had been in support of allowing biosimilars to share generic names, but the sudden removal of a page from the FDA website that contained a 2006 statement supporting same-name biosimilars prompted the concern of the senators. ■

FDA Actions

The FDA is recommending that hydrocodone-containing pain medications (Vicodin, Norco,

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5404. E-mail: neill.kimball@ahcmedia.com.

Lortab, and others) be upgraded from schedule III to schedule II. The move would put significant restrictions on the drugs, including requiring a physician signature for each prescription, no refills, and no phone or fax prescriptions. Hydrocodone would join other powerful opioids including oxycodone, morphine, fentanyl, and methadone in the more restricted schedule II category. The FDA is reacting to the epidemic of prescription drug abuse and addiction that has decimated some communities in this country and has led to the overdose by tens of thousands, including teenagers and young adults. Prescription drug overdoses now outnumber illegal drug overdoses 3:1. The Drug Enforcement Agency has been pushing for stronger controls on hydrocodone for years, but physician and pharmacy organizations have successfully argued that the change unfairly impacts legitimate patients and would increase physician and pharmacy workloads. Hydrocodone/acetaminophen combination drugs were the most frequently prescribed medications in the United States last year. The change is likely to take effect by mid-2014.

Meanwhile, the FDA has approved an extended-release hydrocodone product for the management of severe pain requiring daily, around-the-clock treatment. The drug is an extended-release formulation of hydrocodone that is dosed twice a day. It is available in six strengths — 10, 15, 20, 30, 40, and 50 mg capsules. Because of concerns of addiction and abuse, and the greater risk of overdose and death associated with extended-release and long-acting formulations, hydrocodone extended-release should be reserved for patients in whom alternative treatment options are ineffective, not tolerated, or one otherwise provides inadequate pain management. The approval of hydrocodone extended-release was controversial given that the drug is not packaged as a tamper-proof capsule, theoretically allowing it to be crushed, chewed, or even injected. Experience with abuse of extended-release oxycodone (OxyContin) prompted the FDA to require Purdue Pharmaceuticals to reformulate the drug into a tamper-proof capsule in 2010. Some in the FDA felt this new formulation of hydrocodone should be similarly packaged, but the drug was approved without such restrictions. Hydrocodone extended-release will be schedule II, and marketed by Zogenix Inc. as Zohydro.

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The FDA has approved two new drugs to treat pulmonary arterial hypertension (PAH). Macitentan is a dual endothelin-receptor antagonist, while riociguat is a first in class soluble guanylate cyclase stimulator. Macitentan is a once-daily pill that is approved to treat PAH. Its safety and efficacy was established in a 2-year, randomized, placebo-controlled trial of 742 patients. Patients in the active treatment group had delayed progression of the disease and improved symptoms. Macitentan is manufactured by Actelion Pharmaceuticals and will be marketed as Opsumit. Riociguat is also an oral agent given three times a day. It is approved for PAH and also for chronic thromboembolic pulmonary hypertension (CTEPH), the first drug to be approved for this latter indication. Safety and efficacy for PAH was shown in a trial of 443 patients in which treated patients had improved 6-minute walk times after 12 weeks. It was shown to be effective for CTEPH in a study of 261 patients in which treated patients had improved walk times at 16 weeks. Riociguat is marketed as Adempas by Bayer HealthCare.

An FDA advisory group has recommended approval of simeprevir and sofosbuvir, two long-awaited agents to treat hepatitis C virus (HCV). Both are oral drugs and have higher cure rates compared with currently available agents. Simeprevir is a protease inhibitor, similar to currently available agents such as telaprevir and boceprevir, while sofosbuvir is a new type of hepatitis c antiviral called a nucleotide analogue (or "nuke"). Sofosbuvir has been highly anticipated as clinical trials suggest that it results in sustained virological responses as high as 90%, and may eventually be part of an all-oral regimen for HCV along with ribavirin. The FDA is expected to approve both drugs by mid-December. Simeprevir will be marketed by Johnson & Johnson while sofosbuvir will be marketed by Gilead Sciences. ■