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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.

Headaches That Kill

ABSTRACT & COMMENTARY

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a retained consultant for Boehringer Ingelheim, Merck, and Ortho-McNeil, and is on the speakers bureau for Boehringer Ingelheim.

Synopsis: *Fatal headaches are associated with age over 50, loss of consciousness and collapse, and worst/thunderclap character of the headache.*

Source: Lynch KM, Brett F. Headaches that kill: A retrospective study of incidence, etiology, and clinical features in cases of sudden death. *Cephalalgia* 2012;32:972-978.

THIS STUDY EXAMINED CASES OF SUDDEN DEATH IN WHICH HEADACHE WAS the initial presenting feature. In a retrospective autopsy study, the authors reviewed 55 cases with headache presenting between January 1997 and December 2006 to the Department of Clinical Neurological Sciences, Beaumont Hospital, Dublin. The study population, which was 51% male, ranged in age from 12 to 82 years. The peak incidence of deaths (34.5%) occurred in the 51-70 age group, with 26.7% of that group having multiple medical comorbidities. The number of autopsied deaths per year, with headache as a presenting feature, ranged from 11 (22% of all cases) in 1999, to 1 in 2004, with a mean of 5.5 autopsy cases per year. All 55 patients presented to the emergency room with an associated "red flag" symptom that presumably could indicate potential for an underlying life-threatening etiology for the headache. Red flags that were found in > 20% of patients, ranked from most to least often, were: headache at age > 50 years, seizure/collapse/loss of consciousness, thunderclap headache, worst headache, drowsy/confused/agitated, progressive visual/neurological symptoms, nausea/vomiting, and paralysis/weakness/Babinski sign. The occurrence of a headache in patients > 50 years of age was the most common red-flag feature, presenting in 54.5% (n = 30) of patients. Loss of consciousness or collapse occurred in 52.72% (n = 29); "worst" headache and thunderclap headache in 45.5% (n = 25) and 51% (n = 28), respectively; and nausea and vomiting in 30.9% (n = 17).

VOLUME 31 • NUMBER 4 • DECEMBER 2012 • PAGES 25-32

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There was no correlation between age and the cause of headache-associated death, with the exception of sinus venous thrombosis (SVT) which comprised 8% of the total cause of death associated with headache in the younger age group (median of 40 years). All four cases of SVT occurred in women < 40 years of age with prothrombotic states and with 100% occurrence of two primary red-flag features: a prolonged occipital headache with neck pain and a progressive focal neurological deficit.

The ultimate causes of death found at autopsy in the headache group without evidence of trauma (n = 48) were vascular events in 60.4% (n = 29), primary brain tumors/cysts in 16.7% (n = 8), meningitis in 6.25% (n = 3), and other in 16.7% (n = 8). In cases where aneurysm rupture and subsequent intracerebral hemorrhage were the cause of 20% of headaches (n = 11; male-to-female ratio 1:3), loss of consciousness or collapse, occipital/temporal headache and neck pain, or a focal neurological deficit was the most common red-flag feature in the clinical history.

■ COMMENTARY

Headaches are classified as primary (without any underlying "pathological" cause) or secondary (attributable to vascular, neoplastic, or infectious causes, as well as other intracranial pathologies). Primary headache disorders are very common and neuroimaging cannot be obtained on all patients with headaches unless there are specific concerns in the clinical history and examination. The identification of characteristics of a headache that indicate its potential to be a secondary headache, most commonly a vascular etiology, is very useful in directing a more comprehensive evaluation, including neuroimaging. In this study population, the more statistically significant, alarming red-flag features that ultimately heralded a fatal cause of headache were headaches in those > 50 years of age, headaches described as ''worst''/thunderclap, a history of seizure/collapse/loss of consciousness, and associated nausea and vomiting. However, migraine headaches, which afflict more than 30 million Americans with disability but without mortality, can affect older individuals, can be very severe and of sudden onset, and are characteristically associated with nausea and vomiting. Use of these criteria will still result in imaging of many non-life threatening headaches to catch the rare secondary headaches.

For the clinician caring for patients with headaches, it is worth remembering that primary headaches are most likely to afflict younger patients and that although the pain of migraines can be very severe, the onset of a very severe headache in an older, non-migraineur warrants further investigation, including neuroimaging. This paper suggests that "CT scan should be the initial test of choice for new-onset headache in adults." However, MRI with FLAIR and susceptibility weighted imaging can detect even subtle intracranial hemorrhage as well as other potentially fatal pathologies that could be missed on a CT scan of the head. When feasible, MRI is more sensitive in detecting multiple pathological types.

There are limitations to an autopsy study. Although the decrease in the number of headache-associated deaths over the time of the study was attributed to progressively more accurate diagnosis and effective intervention, decreased referral for autopsy is a plausible cause of the decline in autopsied deaths. Would the conclusions of this study be different if all headache-associated deaths, not just those that were autopsied, had been included? The reliance on autopsies to conclude that headache fatalities are decreasing and the recommendation to do CT scanning over MRI scanning may reflect differences in the health care system in Ireland, as compared to the United States. ■

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media, a division of Thompson Media Group, LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball
VICE PRESIDENT AND GROUP PUBLISHER: Donald R. Johnston

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 105109, Atlanta, GA 30348.

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
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(Student/Resident rate: $125)

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Neurobehavioral and Psychiatric Comorbidities of Epilepsy

ABSTRACT & COMMENTARY

By Nitin K. Sethi, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Epilepsy is associated with behavioral, psychiatric, cognitive, and social comorbidities. The associated comorbidities change across the lifespan of a person with epilepsy. Early detection and treatment of these comorbidities has the potential to significantly improve quality of life for patients with epilepsy.*

Source: Lin JJ, et al. Uncovering the neurobehavioral comorbidities of epilepsy over the lifespan. *Lancet* 2012;380:1180-1192.

The authors searched PubMed (from 1950 to August 2012) and identified all English-language papers that reported on psychiatric, behavioral, and social comorbidities of adult and child epilepsies. An increased prevalence of mood disorders, anxiety disorders, attention deficit disorder, depression, bipolar disorder, panic disorder, and other social phobias was found in children and adults with epilepsy. With respect to children, the increased prevalence of psychiatric and mood disorders was greatest for those with complicated epilepsies (epilepsy plus brain lesions), although even children with uncomplicated epilepsies (normal neuroimaging and normal neurological examination) were not immune. Similarly, cognitive comorbidities (lower scholastic performance, impaired non-verbal intelligence and executive functions) were most evident in children with complicated epilepsies. The authors found social comorbidities in both children (inability to form productive and mutually satisfying relationships) and adults. Adults with epilepsy were more likely to be single and unemployed, and to have lower incomes, lower academic achievements, and higher rates of obesity, inactivity, and smoking.

The authors reported many potential mediators of neurobehavioral and psychiatric comorbidities of epilepsy such as the type of epilepsy syndrome and neuroanatomical anomalies. Temporal lobe epilepsy (TLE) was associated with hippocampal atrophy leading to cognitive deficits in multiple domains of memory and executive functioning, as well as language, while involvement of the orbital frontal cortex and cingulated gyrus in TLE was likely the mediator of psychiatric comorbidities such as depression and psychosis. Children with Rolandic epilepsy were found to have language problems and mild deficits in attention and executive function. Children with epilepsy have altered brain development and connectivity and this likely affects the expression of cognitive, behavioral, social, and psychiatric comorbidities. On the other end of the lifespan, the aging brain is more likely to have a lower baseline cognitive reserve thus predisposing it to cognitive and psychiatric comorbidities of epilepsy. The authors identified core epilepsy-specific characteristics, namely the frequency of interictal epileptiform discharges, the age of epilepsy onset, the duration of the epilepsy, and the cognitive and psychotropic effects of anticonvulsant drug regimens that are likely mediators of neurobehavioral and psychiatric comorbidities of epilepsy. Modification of these core epilepsy characteristics may be one way to treat the neurobehavioral and psychiatric comorbidities of epilepsy.

■ COMMENTARY

As noted in the accompanying editorial,[1] epilepsy is a global health problem and a costly and complex one at that. The cognitive, neurobehavioral, social, and psychiatric comorbidities add to the burden of this common disease. This burden remains, and at times increases, over the lifespan of the individual with epilepsy. Psychiatric and neurobehavioral comorbidities of epilepsy have been well reported in both the psychiatric and neurology literature. This is akin to the chicken and egg causality dilemma. Did the seizure disorder come first followed by the psychiatric and behavioral morbidities or are patients with psychiatric and behavioral disorders more prone to seizure disorders? Whatever the answer to the above question, there is a pressing need to better identify these comorbidities in our patients with epilepsy and to develop epilepsy-specific and individual specific treatment options. ■

Reference

1. Wanted: A global campaign against epilepsy. *Lancet* 2012; 380:1121.

Diabetes and Dementia

ABSTRACT & COMMENTARY

By Michael Lin, MD, PhD

Assistant Professor of Neurology and Neurosciences, Weill Cornell Medical College

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

Synopsis: *Diabetes mellitus is a risk factor for dementia, and poor glucose control is associated with worse cognitive function and greater decline.*

Source: Yaffe K, et al. Diabetes, glucose control, and 9-year cognitive decline among older adults without dementia. *Arch Neurol* 2012;69:1170-1175.

Alzheimer's disease (AD) and strokes (vascular dementia) are the most common causes of dementia in aging, and there is a close relationship between the two. At least half of AD cases at pathology have other significant pathology, most commonly stroke, and at least three quarters of vascular dementia cases have associated AD pathol-

Stroke Alert: A Review of Current Clinical Stroke Literature

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

Stroke Incidence May Be Increasing in Younger People

Source: Kissela BM, et al. Age at stroke: Temporal trends in stroke incidence in a large, biracial population. *Neurology* 2012;79:1781-1787.

Investigators in the Greater Cincinnati/Northern Kentucky Stroke Study reported on their case ascertainment of all strokes in their 1.3 million population base, using a retrospective review of all hospital discharges and medical records. They compared years 1993-1994, and calendar years 1999 and 2005, and stratified patients by age groups. Age, race, and gender-specific incidence rates with 95% confidence intervals were calculated, assuming a Poisson distribution.

The mean age at stroke significantly decreased from 71.2 years in 1993-94 to 69.2 years in 2005 ($P < 0.0001$), and the differences were predominantly due to ischemic stroke rates, not hemorrhagic stroke. The proportion of all strokes under age 55 increased from 12.9% in 1993-94 to 18.6% in 2005. Stroke incident rates in those 20-54 years of age were increased in both black and white patients in 2005 compared to earlier years, and decreased in the elderly groups.

What accounts for these changes over time? The authors postulate increasing risk factors in younger people including obesity, diabetes, drug abuse, hypertension, smoking, and hyperlipidemia, which all increased in the younger population over time. However, one must also consider a false-positive change in age distribution, due to more sensitive neuroimaging techniques, which might increase the frequency of diagnosis without a true change in incidence or prevalence. ■

Cancer May Be a Risk Factor for Ischemic Stroke

Source: Schwarzbach CJ, et al. Stroke and cancer. The importance of cancer-associated hypercoagulation as a possible stroke etiology. *Stroke* 2012;43:3029-3034 .

A history of cancer in a patient with ischemic stroke often raises additional concerns for the clinician, including assessment of cancer activity, as well as possible thrombophilias. The use of thrombolytic agents is also controversial in patients with active cancers. These investigators in Mannheim, Germany, attempted to assess the role of cancer-associated hypercoagulability as a risk factor for stroke by comparing a group of 140 patients with active cancer (solid tumors, excluding hematological malignancies and brain tumors) and ischemic stroke to a group of age- and sex-matched controls who had ischemic stroke without any cancer history. They collected data prospectively, including laboratory data, MRI, etiology and risk factors for stroke, types of cancer, deep vein thrombosis or pulmonary embolism, and D-dimer levels.

One hundred forty stroke/cancer patients were compared to 140 stroke controls. In the cancer patients with stroke, an unidentified cause for stroke ($P < 0.001$) and infarction in multiple vascular territories ($P < 0.001$) were more frequent, and D-dimer levels were significantly higher ($P < 0.05$) in patients with stroke and cancer. In the noncancer stroke patients, conventional risk factors, such as hypertension ($P < 0.05$) and hyperlipidemia ($P < 0.01$), were more common. Deep vein thrombosis and pulmonary embolism were more frequent ($P < 0.01$) and D-dimer levels were higher ($P < 0.01$) in

ogy. There is also a close relationship in their risk factors; many risk factors for stroke — including hypertension, hyperlipidemia, and diabetes — also are risk factors for AD.

This is particularly well illustrated by the recent study from Yaffe and colleagues reporting that diabetes mellitus (DM) and elevated hemoglobin A1c (HbA1c) among those with DM are associated with worse cognition at baseline and greater decline over time. A total of 3069 older adults (mean age 74.2) without dementia were followed prospectively for an average of 9 years at two community clinics in the Health, Aging, and Body Composition (Health ABC) study. DM status and HbA1c were determined at baseline and during follow-up. Cognition was assessed using the modified Mini-Mental State Exam (3MS) and digit symbol substitution test (DSST) at baseline and during follow-up.

At baseline, 23% of participants had prevalent DM, and during follow-up, 5.2% developed incident DM. Prevalent DM was associated with black race, male gender, lower education, history of hypertension or myocardial infarction (MI), and higher body mass index (BMI). After adjustment for all these associations, prevalent DM was still associated with lower baseline 3MS and DSST scores, and with greater decline in 3MS and DSST scores, compared

cancer-associated stroke compared to controls. Lung and pancreatic cancer were significantly overrepresented and manifested higher D-dimer levels compared to patients with stroke and other types of cancer.

This study supports the concept that there is a hypercoagulable state associated with solid tumor cancers, especially in those who have an elevated D-dimer level, and that cancer may be a risk factor for ischemic stroke. The role of antithrombotic therapies in this group of patients is unknown and needs further investigation. ■

Physical Exercise Reduces White Matter Lesion Burden and Brain Atrophy in the Elderly

Source: Gow AJ, et al. Neuroprotective lifestyles and the aging brain. Activity, atrophy, and white matter integrity. *Neurology* 2012;79:1802-1808.

In a longitudinal study of aging in scotland, the investigators examined the impact of physical activity on brain atrophy and white matter lesions (WML) over time. Six hundred ninety-one people born in 1936 were examined and studied by MRI at age 70 and again at age 73. Structural brain biomarkers, including white matter tractography, gray and white matter volume, and WML load, were measured.

At age 73, a higher level of physical activity was associated with higher fractional anisotropy in the white matter, larger gray, and white matter volumes, and a lower WML load, and these associations remained statistically significant after adjustments for covariables, such as age, social class, and health status. Leisure activity, as opposed to physical activity, was not significantly associated with brain biomarkers after adjustment for covariables. In this narrow sample, physical activity was associated with less brain atrophy and WML, but the mechanism is unclear. The investigators are uncertain if physical activity mediates its effects via neuroprotection or a cardiovascular mechanism. ■

Serious Cardiac Arrhythmias May Occur During First 72 Hours After Stroke

Source: Kallmunzer B, et al. Serious cardiac arrhythmias after stroke: Incidence, time course, and predictors — a systematic, prospective analysis. *Stroke* 2012;43:2892-2897.

Investigators of the stroke arrhythmia monitoring Database in Erlangen, Germany, performed continuous telemetric cardiac rhythm monitoring on 501 acute stroke patients admitted to their stroke unit. Arrhythmias were systematically detected and categorized in a prospective fashion, and time of onset and predisposing factors were noted.

Significant cardiac arrhythmias occurred in 25.1% of all patients during the 72 hours of monitoring, with the highest risk period being the first 24 hours after admission. Serious tachyarrhythmias (ventricular or supraventricular arrhythmias > 130 beats per minute) were more frequent then bradyarrhythmias. All arrhythmias were independently associated with higher patient age and higher NIH Stroke Scale scores (more severe stroke). The risk of serious cardiac arrhythmias declines during the first 72 hours after stroke and is at highest risk during the first 24 hours. Patients with more severe strokes and advanced age are at highest risk, and continuous cardiac monitoring is strongly advised during the initial 3 days of hospitalization. ■

to those without DM. Subjects with incident DM tended to have baseline scores and mean declines intermediate between subjects with prevalent DM and those without DM. Among subjects with prevalent DM, higher HbA1c levels (mid and upper tertiles) were associated with lower 3MS and DSST scores than the lowest tertile of HbA1c.

■ COMMENTARY

Other studies have also reported an association between DM and increased risk of cognitive impairment with aging.[1] This was a large prospective study, with a diverse sample and long follow-up, and the results reinforce the notion that maintenance of general health, with particular emphasis on control of vascular risk factors, might reduce the risk of dementia or possibly reduce the rate of cognitive decline in dementia. As an outgrowth of these epidemiological studies, a new trial of intranasal insulin for treatment of early AD has been initiated. ■

Reference

1. Biessels GJ, et al. Risk of dementia in diabetes mellitus: A systematic review. *Lancet Neurol* 2006;5:64-74.

Anti-VEGF Therapies Induce Painful Sensory Neuropathy

ABSTRACT & COMMENTARY

By Norman Latov, MD, PhD

Professor of Neurology and Neuroscience and Director of the Peripheral Neuropathy Center, Weill Cornell Medical College

Dr. Latov has served as a consultant to Grifols, Novartis, CSL Behring, Pfizer, Baxter Biotherapeutics, Elan Pharmaceuticals, and Eisai Inc. He owns stock in Therapath LLC, and is the beneficiary of a licensing agreement between Cornell University and Teva Pharaceuticals.

Synopsis: *The authors provide evidence that vascular endothelial growth factor (VEGF)-receptor inhibitors by themselves can trigger a painful neuropathy and can aggravate paclitaxel-induced neuropathy in mice by interfering with the neuroprotective effects of VEGF. These observations have implication for the use of anti-VEGF agents in cancer patients and for strategies to prevent the development of neuropathy in patients undergoing cancer therapy.*

Source: Verheyen A, et al. Systemic anti-vascular endothelial growth factor therapies induce a painful sensory neuropathy. *Brain* 2012;135:2629-2641.

ANTI-VASCULAR ENDOTHELIAL GROWTH FACTOR (VEGF) agents such as bevacizumab, a monoclonal antibody that neutralizes VEGF, are useful adjunctive agents in cancer chemotherapy, as they interfere with formation of new vessels, thus starving tumor cells. Peripheral neuropathy is a relatively common complication of many chemotherapeutic agents, so that when neuropathy develops in patients treated with both chemotherapy and anti-VEGF agents, the neuropathy usually is attributed to the chemotherapy. However, there is evidence to suggest that anti-VEGF agents by themselves can cause or aggravate the neuropathy. Patients treated with oxaliplatin and bevacizumab, a neutralizing anti-VEGF antibody, have a higher incidence of peripheral neuropathy than those receiving oxaplatin alone, and the anti-VEGF receptor agents sunitinib and sorafenib have been linked to the hand-foot syndrome (a dermatological condition with palmoplantar erythema and edema that is associated with tingling or burning paresthesias) that is caused by small fiber neuropathy.[1,2]

In a transgenic mouse model with altered neuronal VEGF receptor expression, the authors report that VEGF receptor inhibition can by itself induce a painful neuropathy in mice, and that it can aggravate the painful neuropathy caused by paclitaxel. They also show that VEGF can exert direct neuroprotective effects on dorsal root ganglia neurons and that it can counteract the paclitaxel-induced increases in tubulin acetylation. VEGF appears to mediate its neuroprotective effects via the VEGF receptor Flk1 and modulate the activity of the anti-apoptotic protein Bcl2. Since chemotherapy-induced neuropathy adversely affects patients' quality of life and limits the dose or effectiveness of the chemotherapy, the finding that anti-VEGF agents can aggravate the neuropathy has important implications for the use of combination therapies and for the development of strategies to prevent the onset of neuropathy in patients undergoing cancer therapy.

■ COMMENTARY

Excessive levels of VEGF have been implicated in the neuropathy associated with osteosclerotic myeloma or POEMS syndrome,[3] and in diabetic retinopathy or the wet form of age-related macular degeneration.[4] Therapeutic strategies that target neovascularization while sparing the neuroprotective effects of VEGF might be beneficial in those conditions as well. ■

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2. Lipworth AD, et al. Hand-foot syndrome (hand-foot skin reaction, palmar-plantar erythrodysesthesia): Focus on sorafenib and sunitinib. *Oncology* 2009;77:257-271
3. Briani C, et al. Vascular endothelial growth factor helps differentiate neuropathies in rare plasma cell dyscrasias. *Muscle Nerve* 2011;43:164-167.
4. Veritti D, et al. Neovascular age-related macular degeneration. *Ophthalmologica* 2012;227(Suppl 1):11-20.

Piriformis Release Surgery: Beware!

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: *Piriformis syndrome remains an elusive diagnosis and neurologists should avoid recommendations for surgery interventions.*

Source: Justice PE, et al. Piriformis syndrome surgery causing severe sciatic nerve injury. *J Clin Neuromuscul Dis* 2012;14:45-47.

Most descriptions of piriformis syndrome, a controversial entity whereby the piriformis muscle or tendon is hypothesized to compress the sciatic nerve resulting in symptoms that mimic L5 or S1 nerve root compression, antedate modern diagnostic techniques and may actually have represented cases of radiculopathy, plexopathy, or proximal sciatic neuropathy from other causes. In the modern imaging area, when other entities are excluded in patients with otherwise typical sciatica, piriformis syndrome rears its provocative head and when conservative efforts, including injection of the piriformis with anesthetic, corticosteroid, or botulinum toxin, are unsuccessful, transection or release of the piriformis muscle or tendon has been advocated as a relatively safe intervention. This appears to no longer be the case.

Two patients, a 37-year-old man and a 71-year-old woman, underwent piriformis release surgery and, within hours postoperatively, developed severe sciatic neuropathy affecting the peroneal more than tibial innervated muscles in the former, and both branches equally in the latter, with profound weakness and foot numbness which, over several months to a year, demonstrated electrical improvement in the form of reinnervation potentials on needle electromyography, without significant clinical improvement in strength. Intraoperative transection of the nerve was excluded by the presence of the reinnervation potentials, and stretch injury to the sciatic nerve due to blade retraction was suspected. Similar adverse outcomes previously have been reported following surgical intervention for other controversial entrapment neuropathies, including radial tunnel release for radial tunnel syndrome and brachial plexopathy following thoracic outlet surgery, but never following piriformis surgery. Surgeons be forewarned!

■ COMMENTARY

As initially described, one of the cardinal features of piriformis syndrome that is felt to be almost pathognomonic is the presence of a palpable, sausage-shaped mass over the piriformis during an acute exacerbation of pain, which is markedly tender to pressure. One wonders if it is at all possible to palpate a *spindle-shaped* or *sausage-shaped mass* in the piriformis, lying as it does beneath the gluteus maximus, gluteus medius, subcutaneous tissue, and skin? Textbooks describe trigger points, particularly in the lateral third of the muscle near its insertion. Yet, with the tendon having an average diameter of 6.3 mm

at the level of the musculotendinous junction, it stretches the imagination to accept that such as small tendon may be palpated when it lies so deeply. In one autopsy study, 42% of piriformis tendons fused with the obturator internus (and 3% with the gluteus medius). Perhaps piriformis syndrome ought to be alternatively termed obturator internus syndrome. True anatomic piriformis syndrome, if it occurs, is rare. Severe sciatic neuropathy following piriformis section should give one even more pause, before making, and acting on, this illusory diagnosis. ■

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%.
4. After successfully completing the last test of the semester, your browser will be automatically directed to the activity evaluation form, which you will submit online.
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. In this study, which one of the following causes of a fatal headache was seen predominantly in young adult women?
a. Subarachnoid hemorrhage
b. Venous sinus thrombosis
c. Bacterial meningitis
d. Glioblastoma
e. Aqueductal stenosis

2. Which of the following statements regarding temporal lobe epilepsy is true?
a. Temporal lobe epilepsy is not associated with psychiatric comorbidities.
b. Temporal lobe epilepsy is associated with hippocampal atrophy leading to cognitive deficits in the domains of memory, executive functioning, and language.
c. Temporal lobe epilepsy is associated with hippocampal atrophy leading to cognitive deficits in the domains of memory, executive functioning, and language, as well as psychiatric comorbidities such as depression, anxiety disorder, and psychosis.
d. Temporal lobe epilepsy is associated with psychiatric but not neurobehavioral or cognitive comorbidities.

3. Dementia in the elderly is associated with which of the following risk factors?
a. Stroke
b. Hypertension
c. Diabetes mellitus
d. Hyperlipidemia
e. All of the above

4. VEGF has neuroprotective properties on dorsal root gangion neurons.
a. True
b. False

5. Which of the following mimics of piriformis syndrome?
a. L5 radiculopathy
b. S1 radiculopathy
c. Lumbosacral plexopathy
d. Sciatic neuropathy
e. All of the above

6. Risk factors for stroke, such as obesity and diabetes, are increasing in younger people.
a. True
b. False

7. Physical exercise should be avoided by elderly people.
a. True
b. False

8. After acute stroke, bradyarrhythmias are a serious complication.
a. True
b. False

In Future Issues:

Update on Movement Disorders

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

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January–December 2012

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AHC Media

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By Louis Kuritzky, MD

Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Hospital Medicine Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*

VOLUME 17, NUMBER 12 PAGES 23-24 DECEMBER 2012

Beta-Blocker Use in Situations Other than Just Post-MI

Source: Bangalore S, et al. *JAMA* 2012; 308:1340-1349.

Current standard-of-care management of post-myocardial infarction (MI) patients includes long-term use of a beta-blocker, unless otherwise contraindicated. The length of the leash on this concept is not long, however, as prospective data confirming benefits of beta-blockers post-MI are limited to just a few years. Since clinicians have not been given concrete advice about when to *stop* beta-blockers, most patients are kept on beta-blockers indefinitely. Perhaps our indecisiveness is bolstered by anxieties related to the potential consequences of beta-blocker withdrawal in persons with known coronary artery disease (CAD).

In the absence of data from a randomized, prospective, long-term trial, observational data may provide some clues about the relative benefit (or lack thereof) of beta-blockers in at-risk populations. To that end, Bangalore et al report on the outcomes of three different at-risk populations from a CAD registry: post-MI patients (n = 14,043), CAD patients without history of MI (n = 12,012), and patients with CAD risk factors but no known CAD (n = 18,653). Study subjects were enrolled in 2003-2004, and followed for approximately 4 years.

Beta-blocker use was not associated with improved outcomes in *any* of the three subgroups, even the one group we take for granted that there will be beneficial effects: the post-MI group. In the 1990s, the term "cardioprotective" was sometimes used in reference to beta-blockers. Although this may be true for the few short years immediately after an MI where older clinical trials have found a benefit, whether such benefits persist, or extend to other at-risk groups, remains to be determined. ■

Long-Term Sexual and Psychological Adverse Effects of Finasteride

Source: Irwig MS. *J Clin Psychiatry* 2012;73:1220-1223.

Cutaneous dihydrotestosterone is etiologically involved in the development of male pattern baldness. Since finasteride blocks the conversion from testosterone to dihydrotestosterone, it is commonly used to treat the disorder. Systemic alpha-reductase inhibitors like finasteride are occasionally associated with sexual side effects, but only recently has there been the suggestion that finasteride-associated sexual side effects might persist beyond the time treatment is administered. Additionally, recent FDA labeling changes have added depression as a recognized adverse effect of finasteride treatment. Although mechanisms to explain persistent adverse sexual effects are unclear, some animal data suggest persistent diminution in penile relaxation and contraction subsequent to finasteride.

From a population of young men (mean age 31 years) with male pattern baldness (n = 91), Irwig compared men who reported sexual dysfunction for at least 3 months after finasteride cessation to men with male pattern baldness who had not used finasteride. Outcomes of interest were depression scores and suicidal thoughts.

Depression, depressive symptoms, and suicidal thoughts were all substantially more common in the former finasteride users than controls. For example, 75% of former users had a Beck Depression Inventory Score of at least 14 (confirming depression) as opposed to 10% of controls. It is important that clinicians recognize the potential for enduring adverse sexual and psychological symptoms associated with finasteride. ■

Novel CV Risk Markers: How Much Cluck for the Buck?

Source: The Emerging Risk Factors Collaboration. *N Engl J Med* 2012;367:14: 1310-1320.

The c-reactive protein (CRP) debate has no end in sight. While traditional risk stratification tools like the Framingham Risk Score remain well established to distinguish high- and low-risk groups, the intermediate-risk group is the population in which further refinement in risk score might be helpful. Tools like CRP and fibrinogen, when applied to persons of intermediate Framingham risk, might help identify a subgroup that merits consideration for interventions like statins.

The Emerging Risk Factors Collaboration analyzed data from prospective cohort studies (n = 246,669) that included persons free of CV disease at baseline in whom CRP, fibrinogen, and components of Framingham risk score were available. Among persons with an intermediate Framingham risk score (10-20% risk of CV event over the next 10 years), the ad-

dition of either CRP or fibrinogen to risk assessment would result in reclassification of approximately 5% from intermediate to high risk. Such risk status elevation would justify statin treatment. According to current outcomes data, statin intervention in this population would prevent one CV event for every 440 intermediate-risk persons screened. Results were similar for fibrinogen.

The results obtained are "modeled" results rather than actual outcomes. CRP and fibrinogen testing are readily available. Yet, the number needed to test for avoidance of one CV event — more than 400 — is substantial. The authors do not offer an opinion on the *propriety* of such an investigation as CRP or fibrinogen; rather, they simply provide a metric to help quantify how much cluck for the buck one might anticipate. ■

Antidepressants and Auto Accidents

Source: Orriols L, et al. *J Clin Psychiatry* 2012;73:1088-1094.

Driving simulation tests performed with *healthy, non-depressed volunteers* indicate varying degrees of deleterious effect on driving skills with tricyclics (TCA) and mirtazapine, but less so with selective serotonin reuptake inhibitors (SSRIs) and venlafaxine. In direct contrast, but perhaps more pertinent to clinical medicine, trials of driving performance in *depressed patients* on antidepressants suggest better driving skills on SSRIs or mirtazapine than TCAs or venlafaxine. To gain more insight into the effects of antidepressant treatments on auto crashes, Orriols et al reviewed the database of accidents accrued by the French police force from 2005-2008 (n = 210,818).

Being on an antidepressant increased the odds ratio of being the at-fault driver by 34% compared with persons not on antidepressants. The immediate time period around initiation or change of treatment was particularly high risk. Subgroup analysis found the greatest risk among persons receiving serotonin-norepinephrine reuptake inhibitors (e.g., venlafaxine) and the least risk among TCA recipients (e.g., amitriptyline). Even though driving simulation tests suggest that depressed patients who are being treated perform better than untreated patients, clinicians must still exercise vigilance and should consider informing patients — especially upon initiation of or change in treatment — about driving risks. ■

A Different Kind of Fish Story

Source: Rizos EC, et al. *JAMA* 2012;308:1024-1033.

The idea that omega-3 polyunsaturated fatty acids — a.k.a. fish oil — are beneficial stems from *some* positive randomized clinical trials. But the word "some" is limiting in the previous sentence, since some other trials do not report benefit. Rizos et al performed a systematic review and meta-analysis based on 28 studies (n = 68,680) in which adults were treated with omega-3 fatty acids for primary or secondary prevention of cardiovascular disease.

Studies were reported between 1999-2010, and averaged 2 years of follow-up, although some data went as long as 6.2 years. The majority of trials were secondary prevention trials, which — because they represent a higher risk group — might be anticipated to more readily demonstrate risk reduction.

Contrary to popular opinion, this meta-analysis was unable to confirm any positive effects of omega-3 fatty acids, whether the metric was all-cause mortality, cardiac death, sudden death, MI, or stroke. Most of the trials used combinations of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), leaving open the possibility that an EPA or DHA individually might have produced different results. The authors conclude that their data support neither the routine inclusion of omega-3 fatty acids in clinical practice nor guideline recommendations that advocate their use. ■

Risk of Cancer in RA Patients Treated with Disease-Modifying Drugs

Source: Lopez-Olivo MA, et al. *JAMA* 2012;308:898-908.

In the early years of treatment experience with biologic response modifiers (BRMs) for rheumatoid arthritis (RA), concern was raised that the immune-modulating effects responsible for dramatic symptomatic improvement might also lead to increased risk for cancer. Indeed, based on excess cases of lymphoma reported in the Adverse Event Reporting System database among children and adolescents treated with BRMs, the FDA recommended a warning label for all TNF-inhibitors. Should we be worried about cancer risk in patients treated with BRMs?

Lopez-Olivo et al performed a data analysis on randomized, controlled trials (n = 63 trials) of BRM treatment in RA patients in which a BRM was compared with placebo or another traditional therapy such as methotrexate (n = 29,423). A wide variety of BRMs was included in the analysis (e.g., abatacept, adalimumab, anakinra).

This dataset was restricted to trials with at least 6 months' duration. No signal for increased risk of cancer was discerned. Although a trend for increased risk of lymphoma was found, the numbers did not achieve statistical significance. It is not possible to determine whether longer-term outcomes in relation to BRMs will be impacted by cancer risk, since this dataset is comprised of studies of 3 years' duration or less. Additionally, whether RA patients who have already suffered a cancer are at greater risk of recurrence subsequent to BRM treatment is unknown. The dramatic RA disease remission we have come to commonly see thanks to treatment with BRMs appears to be safe from an increased risk for cancer. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
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Menopausal Hormone Therapy and the Risk for VTE, AD

In this issue: Menopausal hormone therapy and risk of VTE and AD; patients' understanding of chemotherapy benefits; and FDA actions.

Hormone therapy and VTE risk

The different drug formulations of menopausal hormone therapy (HT) may determine the risk of venous thromboembolism (VTE), according to a new study. It is known that combined estrogen-progesterone therapy has a higher risk of VTE than estrogen-only therapy, and oral therapy has a higher risk than transdermal therapy. Now, a follow-up study from the Million Women Study with more than 3.3 million patient-years of follow-up looks at the varying risks of different HT combinations. The risk of VTE was again found to be significantly higher for combination estrogen-progesterone therapy compared to estrogen-only therapy (relative risks [RR] = 2.07 [95% confidence intervals (CI) 1.86-2.31] vs 1.42 [1.21-1.66]). Transdermal estrogen-only therapy resulted in no excess risk for VTE (RR 0.82 [0.64-1.06]). Among users of combination estrogen-progesterone, the risk of VTE varied by progestin type with significantly greater risk for preparations containing medroxyprogesterone compared to other progestins (2.67 [2.25-3.16] vs 1.91 [1.69-2.17]; *P* heterogeneity = 0.0007). The risk of VTE was significantly higher (2 times the risk) in the first 2 years after starting combination HT than later years. Five-year risks for pulmonary embolism (PE), both fatal and nonfatal, were calculated as: 1 in 664 for never users of hormone therapy, 1 in 475 for current users of oral estrogen-only, 1 in 390 for users of estrogen-progesterone containing norethisterone/norgestrel, and 1 in 250 for users of estrogen-progestin therapy containing medroxyprogesterone. The authors conclude that VTE risk varies considerably by HT formulation and is greatest in users of oral estrogen-progesterone therapy containing medroxyprogesterone. One case of PE could be avoided for every 1295 current users of oral HT if estrogen-only rather than estrogen-progesterone was used. Among combined HT users, one PE in 700 women could be avoided by use of a progestin other than medroxyprogesterone (*J Thromb Haemost* published online Sept. 10, 2012. doi: 10.1111/j.1538-7836.2012.04919.x). These data follow on the Women's Health Initiative, which also showed a higher risk of breast cancer for combination hormone replacement therapy vs estrogen-only therapy, but this risk is offset by the risk of endometrial cancer in women with an intact uterus on unopposed estrogen. ■

Hormone therapy and AD risk

Does the timing of menopausal HT affect the risk of Alzheimer's disease (AD)? Several studies have suggested the timing of postmenopausal HT is critical, especially during the first 5 years after menopause when hormones appear to be somewhat neuroprotective. The Women's Health Initiative (WHI) study clearly showed that starting HT after age 65 had no effect on cognition and in fact may be harmful. Now a new study confirms that starting HT immediately after menopause may have neuroprotective benefits. In a follow-up from the Cache

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.

County study, 1768 women provided a detailed history on age at menopause and use of HT between 1995 and 2006. During this interval, 176 women developed AD. Women who used any type of HT within 5 years of menopause were at 30% less risk of AD (95% CI, 0.49-0.99), especially if they used it for 10 years or more. By contrast, woman who started HT 5 or more years after menopause did not have a decreased rate of AD. Confirming the WHI findings, rates of dementia were nearly doubled among those who began combination estrogen-progesterone compounds later in life. The authors conclude that the association of HT and the risk of AD may depend on the timing of use. HT appears to be beneficial during the critical window near menopause, but may be associated with an increased risk if initiated later in life. (*Neurology* 2012;79:1846-1852). An accompanying editorial suggests that AD and coronary heart disease share common risk factors. WHI data show that women assigned to HT close to menopause had a reduction in the risk of coronary heart disease, whereas women given HT later in life had increased risk. The same seems to be true for the risk of AD. Two soon-to-be published studies will provide evidence regarding hormone effects on cognition in younger postmenopausal women (*Neurology* 2012;79:1840-1841). The decision to initiate HT in postmenopausal women is generally based on severity of symptoms, risk of breast cancer, risk of venous thromboembolic disease, and other factors. Benefits on cognition and potential protection against AD may now need to be added to the equation. ■

Chemotherapy often misunderstood

Chemotherapy for metastatic lung or colon cancer may provide palliation and prolongation of life by weeks or months, but a new study shows that most patients with these diseases erroneously think that chemotherapy is curative. Researchers studied nearly 2000 patients in the Cancer Care Outcomes Research and Surveillance study who were alive 4 months after diagnosis of stage IV lung cancer or colorectal cancer. All patients received chemotherapy. Overall, 69% of patients with lung cancer and 81% of those with colorectal cancer did not report understanding that chemotherapy "was not at all likely to cure their cancer." This misunderstanding about the benefits of chemotherapy was more prevalent among nonwhite and Hispanic patients as compared to non-Hispanic white patients (odds ratio [OR] for Hispanic patients 2.82, 95% CI, 1.51-5.25; OR black patients 2.93, 95% CI, 1.80-4.78). Patients who rated communication with their physician favorably also had a higher OR (1.90; 95% CI, 1.33-2.72). Educational level, functional status, and the patient's role in decision making were not associated with inaccurate beliefs about chemotherapy. The authors conclude that "many patients receiving chemotherapy for incurable cancers may not understand that chemotherapy is unlikely to be curative." This misunderstanding suggests that patients "have not met the standard for true ongoing informed consent" and may not accept toxic treatment with no reasonable hope of cure. The data also suggest that patients rate their doctors as better communicators if they are more optimistic. The authors suggest that honest communication is "a marker of quality of care" but may cause lower patient ratings (*N Engl J Med* 2012;367:1616-1625). ■

FDA actions

The FDA has approved a new drug for the treatment of chronic myelogenous leukemia (CML). Omacetaxine mepesuccinate is a protein translation inhibitor that was originally identified in the 1970s as a potential treatment for CML as well as other hematologic conditions and even solid tumors. It was eventually dropped from development as the tyrosine kinase inhibitors (TKIs) became the mainstay of therapy. Emerging resistance to imatinib and other TKIs has led to renewed interest in the drug. It was recently approved for chronic, accelerated, or blast-phase Philadelphia-chromosome-positive CML that is resistant or in patients who are intolerant of other therapies including TKIs. Approval was based on a study of patients in chronic or accelerated-phase CML who had been treated with two or more TKIs. Omacetaxine is administered by subcutaneous injection. It is marketed by Teva Pharmaceuticals as Synribo. It joins Pfizer's bosutinib (Bosulif), which also was recently approved for the same indication.

The FDA has approved perampanel as adjunctive treatment for partial onset seizures in patients 12 years of age and older. The drug is the first in its class of noncompetitive AMPA receptor antagonists that are taken orally once daily. Approval was based on data from three Phase 3 studies of nearly 1500 patients with partial-onset seizures which found that perampanel, when used as an adjunctive therapy with other anti-seizure medications, significantly reduced seizure frequency. The drug comes with a boxed warning regarding serious neuropsychiatric events including agitation, aggression, anxiety, paranoia, euphoria, anger, and irritably. Perampanel is marketed by Eisai Inc. as Fycompa. ■