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INSIDE

Financial Disclosure: *Neurology Alert's* editor in chief, Matthew Fink, MD; 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.

Simplifying the Diagnosis of Mitochondrial Myopathy

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: *Fibroblast growth factor 21, an important regulator of glucose and lipid metabolism in muscle, is strikingly elevated in the serum of patients with mitochondrial respiratory chain deficiencies.*

Source: Suomalainen A, et al. FGF-21 as a biomarker for muscle-manifesting mitochondrial respiratory chain deficiencies: A diagnostic study. *Lancet Neurol* 2011;10:806-818.

MITOCHONDRIAL CYTOPATHIES, DISORDERS OF THE MITOCHONDRIAL RESPIRATORY chain, are multisystem disorders, most commonly affecting the peripheral nervous system, presenting as myopathy, but also the central nervous system, endocrine glands, myocardium, eyes, ears, gastrointestinal tract, kidneys, bone marrow, and skin. Myopathy may present at any age, as an isolated syndrome or as one component of a multisystem disorder, with clinical features including chronic progressive external ophthalmoplegia, proximal myopathy, muscle pain, and rhabdomyolysis. Diagnosis is challenging, often requiring both histological and histochemical analysis of muscle tissue to detect ragged-red fibers, subsarcolemmal accumulation of mitochondria, and a mosaic pattern of cytochrome c oxidase (COX) activity, and also necessitating mitochondrial DNA sequencing and nuclear and mitochondrial gene screening. A simpler test may now be at hand.

Fibroblast growth factor 21 (FGF-21), important in the regulation of glucose and lipid metabolism, is a protein whose serum and skeletal muscle concentrations are raised in mice with mitochondrial respiratory chain deficiencies. To determine if this is also true in humans, retrospective measurement of FGF-21 was undertaken in 67 patients, comprising 41 adults and 26 children, whose mitochondrial disorder was confirmed either by DNA analysis (n = 63) or on biochemical or histological analysis (n = 4). Results were compared to FGF-21 levels in 74 healthy and 34 disease controls, age-

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A monthly survey of developments in neurological medicine from the faculty of Weill Cornell Medical College and NewYork-Presbyterian Hospital.

matched wherever possible. Statistical analysis included the Mann-Whitney *U* test, Spearman's rank correlation coefficient, and multivariate regression analyses, using two-sided *P* values with a significance level of $P < 0.05$.

Mean serum FGF-21 concentration was 76 pg/mL in the healthy control group, and did not differ by age or sex. It was 10-fold higher in adults, and an average of 26-fold higher in children, with respiratory chain deficiencies affecting muscle, including complex I, III, or IV deficiency; Alpers' hepatoencephalopathy; or infantile COX deficiency. FGF-21 concentrations were not raised in patients with muscular dystrophies. Sensitivity and specificity of FGF-21 were more than 90% for identifying mitochondrial disease affecting skeletal muscle, and FGF-21 was better than other conventional biomarkers, including lactate, pyruvate, lactate-to-pyruvate ratio, and creatine kinase, for correctly identifying muscle manifesting respiratory chain disorders. Only 3% of the correct diagnoses would have been missed using serum FGF-21 concentrations, whereas 38% would have been missed using lactate and pyruvate, 54% using lactate-to-pyruvate ratio, and 61% using creatine kinase. Serum FGF-21 concentration appears to be the best initial diagnostic test for patients with suspected respiratory chain deficiencies primarily affecting muscle.

■ COMMENTARY

A potent regulator of metabolism, recombinant FGF-21, when administered to rodents and monkeys, produces weight loss, lowering of triglyceride levels, and anti-hyperglycemic effects. How? Evidence suggests it enhances mitochondrial oxidation in adipocytes by activating AMP-activated protein kinase (AMPK) and sirtuin 1 (SIRT1). FGF-21 increases AMPK phosphorylation in mice adipocytes, and increases cellular NAD+ levels, resulting in SIRT1 activation. AMPK and SIRT1 activation induce metabolic genes, and increase oxygen consumption and citrate synthase activity. Hence, FGF-21 regulates mitochondrial activity, enhancing oxidative capacity, through AMPK–SIRT1-dependent mechanisms in adipocytes.[1] ■

Reference

1. Chau MD, et al. Fibroblast growth factor 21 regulates energy metabolism by activating the AMPK-SIRT1-PGC-1alpha pathway. *Proc Natl Acad Sci* 2010;107:12553-12558.

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

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
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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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Variability in Corticobasal Degeneration – A Frontally Dominant Disorder?

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

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

Synopsis: *Cases of autopsy-proven corticobasal degeneration examined in a U.S. academic center presented with frontal-predominant behavioral or cognitive deficits, with a movement disorder following later in the majority.*

Source: Lee SE, et al. Clinicopathological correlations in corticobasal degeneration. *Ann Neurol* 2011;70:327-340.

In this retrospective case series from a San Francisco dementia center, subjects were retrieved from a database and included those with autopsy-proven corticobasal degeneration (CBD; n = 18) based on tau pathology, and also those who met clinical criteria for possible or probable corticobasal syndrome (CBS; n = 40) and subsequently underwent autopsy or brain biopsy (n = 1). Upon chart review of the 18 within the CBD cohort, only 5/18 met clinical CBS criteria at the first visit, and 14/18 at later visits (although 13/13 with long-term follow-up finally met these clinical criteria). Of the 40 with clinically identified CBS, subsequent diagnoses based upon pathol-

ogy were: CBD (n = 14), Alzheimer's disease (AD; n = 9), progressive supranuclear palsy (PSP; n = 5), frontotemporal lobar dementia with TDP-43 protein inclusions (FTLD-TDP; n = 5), mixed (n = 5), Picks' disease (n = 1), and multiple system tau-opathy without argyrophilia (n = 1). Clinically, the autopsy-confirmed CBD cohort fell into four syndromes: executive motor (n = 7), progressive nonfluent aphasia (n = 5), behavioral variant frontotemporal dementia (n = 5), and posterior cortical atrophy (n = 1). There was no difference in survival between the groups. Detailed genetic testing also was performed in a subset of patients, revealing absence of MAPT mutations (8 CBD, 13 CBS) but homozygous presence of the MAPT H1 haplotype in all with CBD (6) and most with CBS (18/19). One patient (mixed FTLD-TDP and AD pathology) had a progranulin mutation. APOE E4 alleles were rare (1/8 CBD). Voxel-based morphometry of brain MRIs demonstrated cortical atrophy in CBD vs controls in the bilateral frontal cortex (including supplementary motor, dorsolateral prefrontal, and pre- and postcentral gyri), as well as the striatum and brainstem. This involvement could be further broken down by syndrome, for example, in executive motor-CBD cell loss focused on perirolandic cortex and striatum, in comparison with posterior cortical atrophy-CBD, which involved temporal and occipital cortical regions, the fusiform gyri, and the left hippocampus.

■ COMMENTARY

Corticobasal degeneration is a rare progressive neurodegenerative disorder commonly diagnosed on the basis of asymmetric, non-levodopa responsive parkinsonism, often accompanied by apraxia, dystonia, and myoclonus, as well as cognitive dysfunction, and is considered to be one of the "Parkinson's-Plus" syndromes. Unfortunately it often is mistaken for Parkinson's disease and other neurodegenerative disorders early in its course, leading to difficulties achieving optimal care in the clinic. Cognitive deficits have been well-described previously.[1] Here, however, the authors expand our understanding of CBD cognitive features, propose a preliminary set of subgroups that may aid in recognition in the clinic, and examine correlations with objective neuroimaging measures. Although some referral bias might be present in this academic dementia center, the authors clearly demonstrate that current CBS clinical criteria have unsatisfactory sensitivity and specificity. It therefore remains the case that many individuals with CBD are misdiagnosed, leading to erroneous counseling, and exposure to the risk of medications that have no proven benefit in CBD. In the clinical arena, the clinical descriptions in this publication therefore may aid in earlier and more accurate diagnosis by raising awareness of these varied (although frontal-predominant) cognitive presentations. In the research arena, one question is whether neuroimaging could have an impact as a diagnostic marker and/or surrogate marker of disease progression. Lack of either currently remains a challenge in clinical trial design. The present study certainly suggests (although does not examine specifically) that MRI data may provide pointers to diagnosis, and it would be fascinating to have long-term data examining performance as a potential biomarker of progression. Finally, should we be lumping or splitting care for our patients with CBD? Many of the "misdiagnoses" are tau-opathies (FTLD, PSP). Some have long-argued that these are variations of a common disease process. Splitting helps dissect the enormous complexity of the disease process itself, and also aids us in the current era of symptom-based interventions for patient management. However, as new treatments become available based upon etiopathogenesis, future treatments conceivably could address tau-opathies as a whole and this may change our way of thinking about these disorders. ■

Reference

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Progressive Multifocal Leukoencephalopathy in Transplant Patients

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Progressive multifocal leukoencephalopathy is a rare complication of immunosupression in patients who undergo organ transplantation, with a high death rate.*

Source: Manteen FJ, et al. Progressive multifocal leukoencephalopathy in transplant patients. *Ann Neurol* 2011;70:305-322.

PROGRESSIVE MULTIFOCAL LEUKOENCEPHALOPATHY (PML) IS a rare viral infection of the central nervous system that affects immunosuppressed patients. PML is caused by viral invasion of oligodendrocytes by the JC virus, leading to progressive multifocal demyelination. PML can occur in patients with HIV, cancer, and after organ transplantation, and also may occur in patients who receive immunosuppressive medications for autoimmune disorders,

Stroke Alert: A Review of Current Clinical Stroke Literature

By Matthew E. Fink, *MD, Interim Chair and Neurologist-in-Chief, Director, Division of Stroke & Critical Care Neurology, Weill Cornell Medical College and New York Presbyterian Hospital*

Direct Thrombin Inhibitors Soon Available to Prevent Stroke in Atrial Fibrillation Patients

Sources: Patel MR, et. al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation (ROCKET AF). *N Engl J Med* 2011;365:883-891. Granger CB, et. al. Apixaban versus warfarin in patients with atrial fibrillation (ARISTOTLE). *N Engl J Med* 2011;365:981-992.

Two recent clinical trials, ROCKET AF and ARISTOTLE, have added two new direct thrombin inhibitors, in addition to dabigatran (RE-LY), to our armamentarium to prevent stroke in patients with atrial fibrillation.

ROCKET AF was designed to test rivaroxaban 20 mg/day in a "non-inferiority" double-blind trial against warfarin (adjusted to INR) in 14,264 patients with nonvalvular atrial fibrillation who were at an increased risk for stroke. The primary endpoints were stroke or systemic embolism, and they occurred in 188 patients (1.7% per year) in the rivaroxaban group and in 241 (2.2% per year) in the warfarin group (hazard ratio [HR] = 0.79; 95% confidence interval [CI] 0.66 to 0.96; $P < 0.001$ for noninferiority). Major and non-major bleeding occurred in 1475 patients in the rivaroxaban group (14.9% per year) and in 1449 patients in the warfarin group (14.5% per year) (HR = 1.03; 95% CI 0.96 to 1.11; $P = 0.44$ NS) with significant reductions in intracranial hemorrhage (0.5% vs 0.7%, $P = 0.02$) and fatal bleeding.

ARISTOTLE was a similar randomized, double-blind trial, comparing apixaban 5 mg twice a day with warfarin (target INR = 2.0 to 3.0) in 18,201 patients with atrial fibrillation and at least one additional risk factor for stroke, testing for noninferiority. The primary outcome (stroke or systemic embolism) was 1.27% per year in the apixaban group compared to 1.60% per year in the warfarin group (HR = 0.79; 95% CI 0.66 to 0.95; $P < 0.001$ for noninferiority; $P = 0.01$ for superiority). The rate of major bleeding was 2.1% per year for apixaban and 3.09% per year for warfarin with the rates of death from any cause 3.52% and 3.94% respectively. The rate of hemorrhagic stroke was less with apixaban.

Both of these studies strongly suggest that the new direct thrombin inhibitors are as good or better than warfarin in preventing ischemic stroke in patients with atrial fibrillation, and appear to have a lower risk of hemorrhagic complications. An unresolved issue with this entire class of agents is that there are no known antidotes, but because they have relatively short half-lives, the anticoagulant effects will wear off in less than 24 hours. Dabigatran (Pradaxa) has been approved by the FDA; rivaroxaban and apixaban are being evaluated by the FDA. ■

Stroke Hospitalizations in Young Adults and Children

Source: George MG, et. al. Trends in stroke hospitalizations and associated risk factors among children and young adults, 1995-2008. *Ann Neurol* 2011 DOI:10.1002/ana.22539.

Investigators from the Centers for Disease Control and Prevention in Atlanta queried the National Inpatient Sample database during the interval from 1995-2008 to determine hospitalization rates for stroke and prevalence of stroke risk factors among children and young adults, from age 5 to age 44 years. Subarachnoid hemorrhage (SAH), intracerebral hemorrhage, and ischemic stroke (AIS) were identified and sorted into seven consecutive 2-year time intervals, and into three age groups — 5-14 years, 15-34 years, and 35-44 years. Cases, risk factors, and comorbidities were identified by

including natalizumab for multiple sclerosis (MS). In this paper, the authors review the literature regarding PML in transplant patients and also attempt to calculate the incidence of PML after heart or lung transplants in a retrospective cohort study.

The authors identified a total of 69 cases of post-transplantation PML; 54 cases from the literature and 15 from the study centers. Of the 69 cases, 44 occurred after solid organ transplant and 25 after bone marrow transplants. The median time to onset of PML symptoms was 11 months after bone marrow transplant and 27 months after solid organ transplant. The median survival after PML diagnosis was 6.4 months in solid organ transplant patients and 19.5 months in bone marrow transplant patients.

The overall case-fatality rate for post-transplant PML was 84% with a 1-year survival of 55.7%. Patients were taking a wide variety of immunosuppressive medications, including steroids and steroid-sparing regimens, and there was no clear association of PML with any individual agent. Patients were treated with many different agents,

ICD-9-CM codes.

During the time interval investigated, the prevalence of hospitalizations for AIS increased among all groups except for females aged 5-14 years. A decrease in hospitalizations from SAH was noted in females aged 15-34 years, and males and females aged 35-44 years. Females aged 5-14 years showed increases for SAH. Traditional stroke risk factors (hypertension, diabetes, obesity, lipid disorders, and tobacco use) were common coexisting conditions and their prevalence increased from 1995-2008, in all groups hospitalized for AIS. Hospitalization for AIS has increased in all age groups of children and young adults and is associated with an increased prevalence of atherosclerotic stroke risk factors. ■

SAMMPRIS Results Published After Enrollment for Intracranial Stenting Trial Was Terminated

Source: Chimowitz MI, et al for the SAMMPRIS Trial Investigators. Stenting versus aggressive medical therapy for intracranial arterial stenosis. *N Engl J Med* 2011;365:993-1003.

In a previous issue of Neurology Alert, we noted that enrollment into SAMMPRIS was stopped after an interval evaluation of the data noted a significantly higher rate of early complications in the "stenting" group compared to medical controls. In this trial, patients with recent TIA or stroke attributed to stenosis of a major intracranial artery (70% to 99%) were randomized to aggressive medical management alone, or aggressive medical management plus percutaneous transluminal angioplasty and stenting (PTAS). The primary endpoint was stroke or death within 30 days after enrollment.

Enrollment was stopped after 451 patients were randomized, because the 30-day rate of stroke or death was 14.7% in the PTAS group (nonfatal stroke = 12.5%; fatal stroke = 2.2%) and 5.8% in the medical management group (non-fatal stroke = 5.3%; non-stroke-related death = 0.4%). Beyond 30 days, stroke in the same territory occurred in 13 patients in each group. Follow-up is continuing with a mean of 11.9 months. The probability of occurrence of the primary endpoint over time differed significantly between the two treatment groups at 1 year, with 20.0% in the PTAS group and 12.2% in the medical management group. The differences between the groups can be explained by a higher than expected risk in the placement of intracranial stents, and a lower than expected risk with aggressive medical management. ■

Severe Carotid Artery Stenosis Does Not Appear to be a Significant Risk Factor for Stroke in Patients Undergoing Coronary Artery Bypass Surgery

Source: Mahmoudi M, et al. Patients with severe asymptomatic carotid artery stenosis do not have a higher risk of stroke and mortality after coronary artery bypass surgery. *Stroke* 2011;42:2801-2805.

The authors performed a retrospective analysis of 878 patients with documented carotid duplex ultrasound who underwent isolated coronary artery bypass surgery at Washington Hospital Center in D.C. from 2003 to 2009 and compared those with severe (> 50% stenosis) asymptomatic carotid artery stenosis (CAS) (n = 117) to those without severe CAS (n = 761) for rates of stroke and death while hospitalized.

Patients with severe CAS were older and had more comorbidities, but had similar rates of in-hospital stroke (3.4% vs 3.6%) and mortality (3.4% vs 4.2%) compared with patients without severe CAS. In addition, the 30-day rate of mortality was also similar between the two groups. ■

including cytosine arabinoside, mirtazapine, mefloquin, and cidofovir, and reduction of immunosuppressive medication dosing had no clear beneficial effect from any of the specific therapies tried.

One of the centers calculated an incidence of PML in post-heart and/or lung transplant patients by reviewing charts of all transplanted patients since 1988. Three cases were identified in 427 total patients, for a calculated incidence rate of 1.24 cases per 1,000 post-transplantation person-years.

■ **COMMENTARY**

PML is a rare but devastating demyelinating illness that was a major concern in the height of the AIDS era in the 1980s. More recently, neurologists have been interested in PML because of its association with natalizumab therapy in patients with MS. The incidence of PML in MS patients treated with natalizumab is approximately one case per 1000 person-years, and in HIV patients on highly active antiretroviral therapy, the incidence is six cases per 1000. Since the 1950s, sporadic cases of PML have been report-

ed in patients with leukemia and the first case reported after an organ transplant was in 1974.

This study makes a number of important observations. First, in patients who have undergone heart and/or lung transplants, the risk of PML is similar to the risk in MS patients treated with natalizumab. The numbers are quite low overall (three cases in the cohort), but clinicians should consider PML as a possible diagnosis for patients who develop new neurological deficits and have supportive imaging. Second, the latency of PML after transplantation can be quite long, so clinicians should not exclude the possibility of PML even one or more years post-transplant. The mortality of this disease remains quite high and more research into effective therapies is needed. ■

Neurological Injury in Adults Treated with Extracorporeal Membrane Oxygenation

ABSTRACT & COMMENTARY

By Halinder S. Mangat, MD

Assistant Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Extracorporeal membrane oxygenation is associated with a high mortality and a high incidence of neurological complications including stroke, subarachnoid hemorrhage, and brain death.*

Source: Mateen FJ, et al. Neurological injury in adults treated with extracorporeal membrane oxygenation. *Arch Neurol* 2011; Epub ahead of print. doi:10.1001/archneurol.2011.209.

EXTRACORPOREAL MEMBRANE OXYGENATION (ECMO) IS A mechanism for external mechanical blood oxygenation. It is reserved for patients who suffer acute severe respiratory failure and have failed maximal conventional management. The cause of the respiratory failure may be primarily lung related or of cardiac origin.

ECMO was first investigated as early as 1954.[1] It traditionally has been used in children, but with improved technology ECMO now increasingly is employed in adults. However, the morbidity and mortality remain high due to the severity of the underlying diseases.

Mateen et al review the neurological outcomes in adult patients undergoing ECMO in a single institution over an 8-year period. Eighty-seven patients were treated with ECMO; the main indications for ECMO were post-cardiopulmonary arrest and post-cardiotomy respiratory failure. Survival was 52% at 7 days and 44% at 30 days after ECMO was discontinued. Patients who did not have CPR prior to ECMO survived longer (19 days vs 15 days in those who had CPR). Withdrawal of support occurred in 36% of patients who underwent ECMO.

Neurological complications occurred in 50% of patients and included new onset coma of varying degrees. Coma was attributed to anoxic brain injury, metabolic encephalopathy, or undefined cause, and all three conditions occurred with similar incidence. There were a smaller number of patients who suffered strokes and brain death.

Neuroimaging was abnormal in 15 of 24 patients studied. Autopsy consistently demonstrated pathological findings of hypoxia-ischemia and hemorrhage (9/10 patients).

■ COMMENTARY

ECMO is a life-saving intervention that can be used in various clinical scenarios. In the H1N1 epidemic in Australia-New Zealand, more than 200 predominantly young adults were treated for severe acute respiratory distress syndrome. More than one-third received ECMO and mortality was 21%.[2] ECMO also has been used to transport patients to tertiary centers when use of conventional mechanical ventilation was not deemed safe.[3] And more recently, the use of ECMO after in-hospital cardiac arrest showed improved outcomes.[4] Patients can be supported on ECMO while awaiting lung transplant.

There are numerous factors that determine outcome after a severe illness requiring ECMO. Most important is the underlying cause of cardiorespiratory failure as well as pre-morbid state. In this cohort, patients who received CPR had worse outcome. This may well be related to the cardiopulmonary arrest than ECMO. Furthermore, anticoagulation can lead to intracranial hemorrhage just as in patients who are anticoagulated for reasons other than use of ECMO. This may manifest as intracerebral, intraventricular, or subarachnoid hemorrhage.

Brain imaging abnormalities appear to be more common in patients undergoing venoarterial ECMO than those undergoing venovenous ECMO.[5] This might suggest a causative role for arterial cannulation and manipulation. With newer techniques, complications may be reduced. Javidfar et al[6] report the use of a bicaval dual-lumen catheter for veno-venous ECMO. This allows access via only one site (internal jugular), reduces recirculation, and allows the patient to participate in physical therapy and be more mobile.

Of note in the above study is that not all patients were examined by a neurologist during their illness in the intensive care unit. Given the high incidence of neurological complications from a singular intervention, it would appear that neurological consultation be sought early on

to assess the neurological effect of the precipitating illness. This will help detect new neurological signs while the patient remains on ECMO and will help treat and offset further complications. ■

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United States Postal Service

Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication Number	3. Filing Date
Neurology Alert	0 7 4 1 – 4 2 3 4	10/1/11
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305
Contact Person: Robin Salet
Telephone: 404-262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not printer)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do not leave blank)*

Publisher *(Name and complete mailing address)*
James Still, President and CEO
AHC Media LLC, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

Editor *(Name and complete mailing address)*
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Full Name	Complete Mailing Address
Thompson Publishing Group Inc.	805 15th Street, NW, 3rd Floor, Washington, D.C. 20005

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PS Form **3526,** October 1999 *(See Instructions on Reverse)*

13. Publication Title: Neurology Alert			14. Issue Date for Circulation Data Below: September 2011	
15. Extent and Nature of Circulation			Average No. Copies Each Issue During Preceding 12 Months	No. Copies of Single Issue Published Nearest to Filing Date
a. Total Number of Copies *(Net press run)*			885	854
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	613	620
	(2)	Paid In-County Subscriptions Stated on Form 3541 *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	47	58
	(4)	Other Classes Mailed Through the USPS	26	4
c. Total Paid and/or Requested Circulation *[Sum of 15b. (1), (2),(3),and (4)]*			686	682
d. Free Distribution by Mail *(Samples, compliment ary, and other free)*	(1)	Outside-County as Stated on Form 3541	22	22
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f. Total Free Distribution *(Sum of 15d. and 15e.)*			42	42
g. Total Distribution *(Sum of 15c. and 15f)*			728	724
h. Copies not Distributed			157	130
i. Total *(Sum of 15g. and h.)*			885	854
j. Percent Paid and/or Requested Circulation *(15c. divided by 15g. times 100)*			94%	94%

16. Publication of Statement of Ownership
☑ Publication required. Will be printed in the November 2011 issue of this publication. ☐ Publication not required.

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PS Form **3526,** October 1999 *(Reverse)*

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. Recent evidence suggests that the most sensitive marker for suspected respiratory chain deficiencies primarily affecting muscle is:

a. pyruvate.
b. lactate.
c. lactate-to-pyruvate ratio.
d. serum fibroblast growth factor 21 (FGF-21) concentration.
e. All the above are equally sensitive

2. All of the following regarding progressive multifocal leukoencephalopathy (PML) are true *except*:

a. The JC virus has been firmly established as the cause for PML.
b. PML is a demyelinating disorder of the central nervous system.
c. PML may occur in any condition associated with immune-system suppression.
d. Following organ transplant, PML can be prevented by selecting a “safe” drug regimen.
e. PML in patients with MS is associated with the use of natalizumab therapy

3. Features of corticobasal degeneration include all *except*:

a. neuronal aggregates comprising tau protein.
b. alpha-synuclein deposition in neurites and neuronal cell bodies.
c. progressive non-fluent aphasia.
d. behavioral variant frontotemporal dementia.
e. posterior cortical atrophy.

4. Use of extracorporeal membrane oxygenation is associated with a high prevalence of coma and death.

a. True
b. False

5. The prevalence of hospitalizations for ischemic stroke in children and young adults has been increasing over recent decades.

a. True
b. False

6. The direct thrombin inhibitors, rivaroxaban and apixiban, have been approved by the FDA for prevention of stroke in patients with atrial fibrillation.

a. True
b. False

7. Intracranial stenting is safe and effective as a treatment for stroke attributed to intracranial arterial stenosis.

a. True
b. False

8. Severe asymptomatic carotid artery stenosis does not increase stroke risk in patients undergoing coronary artery bypass surgery.

a. True
b. False

In Future Issues: **Update on Multiple Sclerosis**

PHARMACOLOGY WATCH

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

Medication Poisonings Are Increasing in Children

In this issue: Medication poisonings in children; rosuvastatin vs atorvastatin for atherosclerosis; saw palmetto for prostate symptoms; using atypical antipsychotics for off-label indications in adults; and FDA actions.

More medications, more poisonings

Medication poisonings among young children have increased in frequency in recent years despite safety measures to prevent them, according to a new study from *Pediatrics*. Researchers used patient records of more than 450,000 children 5 years old or younger from 2001-2008. The rate of poisoning increased by about a third during this time span compared to the prior decade. Child self-exposure was responsible 95% of the time with ingestion of prescription drugs causing more than half of the poisonings and more than 70% of significant injuries. The most dangerous drugs were opioids, sedative-hypnotics, and cardiovascular agents. The authors conclude that the number of children visiting emergency departments after medication exposure is increasing, with the majority of ingestions caused by children finding and ingesting medications by themselves. They suggest that efforts at poison-proofing homes with young children "may be a good, but insufficient, strategy." They further suggest that the increase in poisonings is in part due to the rise in number of medications in the environments of young children, with the number of adults taking medications, especially opioid medications, rising dramatically in the last 10 years. Other possible explanations include more siblings on medications, especially ADHD meds, as well as exposure to grandparents' homes where child-proofing may not be as rigorous. They further conclude that current preventive efforts are inadequate and new measures, such as efforts targeting home medication safety (including storage of medications and child-resistant closures) and repackaging (such as blister packs and flow restrictors on liquid medications), should be considered. (*Pediatrics* published online September 16, 2011.) ■

Rosuvastatin no better than atorvastatin

Rosuvastatin is no better than atorvastatin in slowing progression of coronary atheroma, according to AstraZeneca, the manufacturer of rosuvastatin and sponsor of the study. Researchers compared rosuvastatin 40 mg to atorvastatin 80 mg in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin vs Atorvastatin (SATURN) trial. The primary efficacy endpoint was change from baseline in percent atheroma volume in a targeted coronary artery as assessed by intravascular ultrasound. After 104 weeks of treatment in some 1300 patients, there was a numerical greater reduction in favor of rosuvastatin, but the reduction did not reach statistical significance (astrazeneca.com/Media/Press-releases). The full results will be presented at the American Heart Association meeting in

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November. The results come as a blow to the manufacturer of rosuvastatin (Crestor) who had hoped to gain a marketing advantage before the introduction of low-cost generic atorvastatin into the market, slated for December. ■

Saw palmetto for prostate symptoms

Saw palmetto is ineffective for treating lower urinary tract symptoms (LUTS) in men with benign prostatic hyperplasia (BPH), even at higher doses, according to a new study. Previous studies have shown no benefit from saw palmetto, but researchers in this current study set out to test the efficacy of 2-3 times the normal daily dose on men over the age of 45 with significant LUTS. The main outcome was the difference in American Urologic Association Symptom Index score between baseline and week 72. Both saw palmetto and placebo led to an improvement in symptoms with a favorability toward placebo regardless of the dose of saw palmetto. Doses tested were a single 320 mg tablet per day with dose escalation to 2, then 3, tablets per day. The authors conclude that increasing doses of saw palmetto root extract did not lower LUTS more than placebo in men with BPH (*JAMA* 2011;306:1344-1351). This is the second rigorously controlled trial after the Saw Palmetto Treatment for Enlarged Prostates study (*N Engl J Med* 2006;354:557-566) to show no benefit from the supplement on LUTS in men with BPH. ■

Off-label use of atypical antipsychotics

Controversy surrounds the use of atypical antipsychotics for off-label indications in adults, especially the elderly with dementia. A new meta-analysis reviews the evidence of efficacy of these drugs for various off-label uses. Of more than 12,000 studies considered, 162 were included in the analysis. Drugs reviewed included risperidone (Risperdal), olanzapine (Zyprexa), quetiapine (Seroquel), aripiprazole (Abilify), ziprasidone (Geodon), asenapine (Saphris), iloperidone (Fanapt), and paliperidone (Invega). For elderly patients with dementia, a small but statistically significant improvement in symptoms such as psychosis, mood alterations, and aggression were seen with aripiprazole, olanzapine, and risperidone. For generalized anxiety disorder, quetiapine was the most effective, while for obsessive-compulsive disorder, risperidone was associated with a 3.9 greater likelihood of favorable response, compared with placebo when used with antidepressants. There was no benefit seen with any of the drugs used in treating eating disorders, substance abuse, or insomnia, and only marginal benefit in personality disorders or posttraumatic stress disorder. All of these drugs have a boxed warning regarding increased mortality in elderly patients with dementia and increased risk of suicidality. Increased risk of death was seen in elderly patients with a number needed to harm (NNH) of 87. Also noted was increased risk of stroke, especially with risperidone (NNH = 53), extraparametal symptoms (NNH = 10 for olanzepine, NNH = 20 for risperidone), and urinary tract symptoms (NNH range = 16-36). Weight gain was also a problem in non-elderly adults, particularly with olanzapine (incidence of more than 40%), while akathisia was more common with aripiprazole. Other common side effects included fatigue, sedation, and extrapyramidal symptoms. (*JAMA* 2011;306:1359-1369). ■

FDA actions

The FDA has issued a warning regarding the potential for arrhythmia associated with the antinausea drug ondansetron (Zofran). The drug should be avoided in patients with QT prolongation as they are at particular risk of developing torsade de pointes. Ondansetron should be used with caution in patients with congestive heart failure, bradyarrhythmias, those predisposed to low potassium or magnesium, and in those taking drugs that cause QT prolongation. These patients should have electrocardiogram monitoring if ondansetron is indicated. The FDA is requiring new labeling changes to reflect these warnings.

The FDA is reminding physicians and patients that epinephrine inhaler (Primatene Mist), the only over-the-counter inhaler for asthma, will be removed from the market on December 31. The withdrawal is due to an international ban on chlorofluorocarbon propellant. The FDA is recommending that physicians ask their patients with asthma if they use Primatene Mist and talk to them about prescription alternatives.

The FDA has approved infliximab (Remicade) to treat moderate-to-severe ulcerative colitis (UC) in children 6 years and older who have had inadequate response to conventional therapy. The drug is already approved for adults with UC. The approval was based on a randomized, open-label trial of 60 children ages 6 to 17 with moderate-to-severe UC. The drug carries a boxed warning for serious infections and cancer. Infliximab is manufactured by Janssen Biotech. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

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 16, NUMBER 11 PAGES 21-22 NOVEMBER 2011

How Often Do You Really Have to See Patients on Warfarin?

Source: Rose AJ, et al. *Chest* 2011;140: 359-365.

IT HAS BEEN CUSTOMARY TO ASK PATIENTS on warfarin, once controlled and stable, to return on a monthly basis for recheck. This interval has been based on tradition, rather than any firm scientific basis. Frequent visits in otherwise stable patients present a significant burden of time, cost, inconvenience, and even the opportunity for overzealous "fine tuning," and may not enhance the amount of time spent in the therapeutic range. It would, therefore, be desirable to have better insight into whether stable patients might be safely allowed longer intervals without risking either toxicity of supratherapeutic warfarin dose, or thrombotic risk of subtherapeutic levels.

Rose et al report on data obtained from a large population of persons receiving anticoagulation from the U.S. Veterans hospital system (n = 104,451). By comparing the interval between an in-range international normalized ratio (INR) and the next INR measurement with the likelihood of being in the therapeutic range on follow-up visit, they were able to discern that the first two visits after a therapeutic INR measurement are time sensitive: that is, extending the time until next follow-up beyond 4 weeks was associated with progressively greater likelihood of finding an out-of-range INR at the next visit. This relationship, however, was not seen in persons with consistently in-range INR readings, i.e., if a patient had experienced three consecutive INR in-range visits, extending the length of time until next follow-up was not associated with greater likelihood of an out-of-range INR.

At the current time, another trial comparing monthly with quarterly INR monitoring is underway. Pending results from that trial, this evidence suggests that until patients have at least three consecutive stable INR measurements, the traditional 4-week return policy is best. After that, a longer interval until next INR measurement is acceptable, but has only been studied as far out as 38 days. ■

Replacing Carbohydrates with Nuts in the Diabetic Diet

Source: Jenkins DJ, et al. *Diabetes Care* 2011;34:1706-1711.

CONSUMPTION OF NUTS, ESPECIALLY WALnuts, has been associated with favorable health outcomes. For diabetics, maintenance of a healthy body weight, reduction of high-glycemic index foods, and lipid modulation through diet are each a potentially critical consideration. Because nuts have significant fat content, there has been concern that were diabetics to substitute nuts for other carbohydrates, a detrimental impact on either weight or lipids might be seen.

Jenkins et al randomized type 2 diabetics (n = 117) to substitute carbohydrates in their diets in one of three ways: mixed nut replacement, muffin replacement, or half-and-half nuts plus muffins. Based on energy requirements calculated with the Harris-Benedict equation, participants were asked to substitute their prescribed replacement supplement for whatever carbohydrate had previously comprised an equal caloric proportion of their diet. For instance, a person requiring 1600-2400 kcal/d was given 475 kcal of a replacement supplement. The trial lasted 3 months. The nut mix consisted of almonds, pistachios, walnuts, pecans, hazelnuts, peanuts, cashews, and macadamias. The muffin was whole wheat, with no sugar added. The absolute kcal content of the supplement was the same whether administered as nuts, muffin, or mixed.

The group supplemented with nuts enjoyed a statistically significant A1c reduction of 0.21%, but no significant A1c change was seen in the other two groups. Similarly, cholesterol, LDL, and cholesterol:HDL ratios were most favorably affected by the nut supplement. Nut replacement for carbohydrates has favorable effects in type 2 diabetes. ■

Hypertensive Emergency: The Prognostic Value of Elevated Troponins

Source: Afonso L, et al. *J Clin Hypertens* 2011;13:551-556.

HYPERTENSIVE EMERGENCY, CHARACTERized by marked elevation of blood pressure (typically > 180/120) associated with signs of target organ damage, is a common presenting issue in emergency departments. Since cardiac toxicity may be one of the signs of target organ damage, troponins are often measured, even though there may be no symptoms of myocardial ischemia or signs on EKG. Especially when troponins are measured in acute coronary syndromes, they have strong prognostic value. Whether they provide any discriminative value in per-

sons with hypertensive emergency has not been previously well-studied.

A retrospective analysis was done on all patients with hypertensive emergency seen at two inner-city population hospitals in Detroit (n = 567) in whom troponins had been measured. Among this group, one-third demonstrated troponin elevation (mean peak = 4.06 ng/mL). However, follow-up of these patients did not find that the presence or degree of elevation of troponins predicted subsequent mortality over the next 3 years.

Elevation of troponins is commonly seen in patients with hypertensive emergency, but in the absence of an acute coronary syndrome, is not prognostically valuable. ■

Is Mercury Really a Bad Guy in CV Disease?

Source: Houston MC. *J Clin Hypertens* 2011;13:621-627.

Mercury has a bad rap sheet: it decreases cellular oxidative defenses, increases oxidative stress, reduces the effectiveness of metalloenzymes, induces mitochondrial dysfunction, increases vascular inflammation, and worsens endothelial function. In addition, mercury toxicity is associated with increased carotid intima-media thickness. Omega-3 fatty acids, as contained in fish, can antagonize some of the detrimental effects of mercury. However, fish in the diet are also currently the major source of human exposure to mercury.

There is no known biologic or physiologic role of mercury in the body, hence it must be regarded as a toxin.

Observational data generally, but inconsistently, find an association between tissue levels of mercury and cardiovascular disease. For hypertension particularly, numerous different populations have found a relationship between tissue mercury levels and blood pressure (systolic, diastolic, and pulse pressure). Chronic mercury toxicity may be inexpensively measured by a 24-hour urine mercury level. The author does not include mention of any trials indicating favorable effects achieved by modulation of mercury, although selenium, by complexing with mercury, may mollify some of its toxic effects. ■

Long-Term Azithromycin for Prophylaxis of COPD Exacerbations

Source: Albert RK, et al. *N Engl J Med* 2011;365:689-698.

For many patients with moderate-severe chronic obstructive pulmonary disease, acute exacerbations (AECOPD) are highly problematic. For hospitalized AECOPD, the mortality rate is approximately 10%; loss of pulmonary function that typically accompanies an AECOPD is usually not regained; mortality during the year following an AECOPD is increased. Hence, reduction and/or delay of AECOPD is an important goal.

Macrolides are often the antimicrobial agents chosen to treat AECOPD. This trial in patients with COPD randomized subjects to azithromycin 250 mg qd (n = 570) or placebo (n = 572) for 1 year. The patient's background COPD treatments were unchanged. The primary outcome of the trial was time to first AECOPD. Secondary outcomes included QOL, and scores on the St. Georges Respiratory Questionnaire. More than three-fourths of study participants were receiving background inhaled steroids, long-acting beta agonists, and/or long-acting anticholinergics during the trial.

Azithromycin prophylaxis was associated with a statistically significant prolongation of time to first AECOPD, as well as a 27% relative-risk reduction in the frequency of AECOPD. The St. George's Respiratory Questionnaire scores were improved significantly more in the azithromycin group. One adverse effect analyzed was affect on hearing function: Azithromycin was associated with a slightly higher incidence of hearing decrement than placebo. However, improvements in hearing noted on follow-up occurred whether the drug was discontinued, suggesting that perhaps the incidence of hearing decrements were initially overestimated.

Azithromycin prophylaxis may provide important benefits in COPD, especially for persons with frequent AECOPD. ■

Unintended Medication Consequences of Hospital Admission

Source: Bell CM, et al. *JAMA* 2011;306: 840-847.

Most hospitalizations have a focused agenda: heart failure, pneumonia, acute trauma, etc. It is not at all difficult to conceive that as a consequence of intensified focus on one or more often acute problems, attention can be drawn away from the issues of lesser acuity, such as maintenance medications for dyslipidemia, dysglycemia, or thyroid disease. Sometimes because of discontinuity between persons involved in the patient's hospitalization and outpatient providers, inadvertent discontinuation of necessary chronic medications can be overlooked.

Using the database of patients in Ontario, Canada (n = 396,380; age 66 and older), Bell et al examined prescription data to see whether chronic medications from five different classes experienced discontinuation subsequent to hospitalization. The five classes were: statins, antiplatelet/anticoagulants, levothyroxine, respiratory inhalers, and gastric acid inhibitors.

Hospitalization was associated with an increased incidence of discontinuation of all five classes of agents. Hospitalization, which included ICU admission, was disproportionately likely to be associated with chronic medication discontinuation. Equally distressing, the data demonstrated an increased risk for death or subsequent hospitalization in persons who discontinued their chronic medications. Gaps in continuity of care are of significant consequence to hospitalized patients. ■

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

Executive Editor: Leslie Coplin.
Editor: Stephen Brunton, MD.
Managing Editor: Neill L. Kimball.
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