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INSIDE

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Nigrostriatal Dopaminergic System and REM Sleep Behavior Disorder

ABSTRACT & COMMENTARY

By Charles P. Pollak, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *REM sleep behavior disorder may be an early manifestation of a more generalized neurodegenerative disorder that involves the nigrostriatal system.*

Source: Kim YK, et al. The implication of nigrostriatal dopaminergic degeneration in the pathogenesis of REM sleep behavior disorder. *European J Neurology* doi:10.1111/j.1468-1331.2009.02854.x.

REM SLEEP BEHAVIOR DISORDER (RBD) IS AN INTRIGUING DISORDER of older men (mainly) who enact dreams that are uniquely active and violent. Violent behavior during sleep may result from the loss of normal inhibition of motor systems during REM sleep. RBD may herald the development of neurodegenerative disorders (synucleinopathies) such as Parkinson disease (PD), multiple system atrophy (MSA), and Lewy Body dementia (DLB). The pathogenesis of RBD is therefore of particular interest.

One question concerns the role of the nigrostriatal dopaminergic system in the pathogenesis of RBD. The pharmacologic evidence is confusing. RBD readily responds to clonazepam, but that agent has no clear effects on dopamine neurotransmission. By contrast, pramipexole (Mirapex) is known to be a full D_2-D_4 agonist, but is ineffective in RBD associated with PD.

To clarify any role of dopamine physiology in RBD, investigators at Seoul National University in Korea subjected three groups of subjects to single-photon emission computer tomography (SPECT) after injection of [^{123}I]FP-CIT. The groups were 14 patients with idiopathic RBD, 14 patients with PD and 12 normal controls. Group differences of [^{123}I]FB-CIT uptake were significantly depressed for the putamen as a region of interest (ROI) and for the caudate/putamen ratio. Puta-

Weill Cornell Medical College

NewYork-Presbyterian

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

menal uptake was lowest for the PD group and intermediate for the RBD subjects. No significant correlation was observed between EMG activity during REM sleep and dopamine transporter (DAT) densities. The investigators interpret this to mean that there was no relation between DAT density and the severity of RBD. They suggest that a pathway other than the nigrostriatal dopaminergic one exists but the identity of this alternate influence on polysomnographic EMG activity is not identified.

■ COMMENTARY

This is not the first time brain scanning has been used to assess dopaminergic function in RBD, but the samples reported here may be the largest to date. The findings are consistent with those of earlier studies, namely decreased striatal binding in RBD compared with healthy controls, though not PD. The observation that RBD often heralds the development of neurodegenerative disorders with parkinsonism is consistent. As is well known, RBD also accompanies established PD along with other, often severe sleep difficulties of the sleep-maintenance type. This may occur independent of any medications used to treat PD and is not simply a dopaminergic effect.

Clearly, the time is long past when PD or other neurodegenerative disorders can be managed without taking a careful sleep history and performing an overnight sleep recording to assess the EMG component for signs of disinhibition as well as the respiratory component for signs of sleep apnea. ■

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ASSOCIATE PUBLISHER: Coles McKagen
MANAGING EDITOR: Allison Weaver
DIRECTOR OF MARKETING: Schandale Kornegay

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Questions & Comments

Please contact **Allison Weaver**, Managing Editor, at allison.weaver@ahcmedia.com, or (617) 629-5951.

Functional Neuroanatomy of Gerstmann Syndrome

ABSTRACT & COMMENTARY

By John J. Caronna, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Gerstmann Syndrome is associated with lesions of the parietal cortex and subcortical white matter in the region of the angular gyrus. It should be considered one of the "disconnection" syndromes.*

Source: Rusconi E, et al. A disconnection account of Gerstmann syndrome: Functional neuroanatomy evidence. *Ann Neurol* 2009;66:654-662.

FROM 1924 TO 1930 IN VIENNA, JOSEF GERSTMANN PUBlished three case reports describing patients with finger-agnosia, dysgraphia, dyscalculia, and right-left disorientation. He asserted that these four symptoms constituted an independent syndrome and were the expression of disease in the left angular gyrus where, he postulated, there was a common functional denominator essential to these four cognitive faculties.

Since Gerstmann's description, authors who have studied the clinico-anatomic correlations of the syndrome found that the lesions, although always in the dominant hemisphere, were not restricted to the angular gyrus, and that the four components of Gerstmann syndrome usually were not an autonomous entity but part of many concurrent deficits including impaired recent memory, visual field defects, aphasia, and emotional lability.[1]

Based on the failure of intraoperative electrostimulation to identify a single site where disruptive stimulation would elicit all four symptoms,[2] the current view is that there is no functional association of the four domains that fail in Gerstmann syndrome.

The present authors also sought to determine whether a shared cortical site existed that could account for a pure Gerstmann syndrome. They used functional magnetic resonance imaging (fMRI) in five healthy, right-handed subjects (four men, one woman, mean age 21 years) to study cortical activation patterns during each of the four tasks: calculation, left-right orientation, finger gnosis, and writing. Each task was repeated in two sepa-

rate sessions for a total of eight sessions per subject.

None of the subjects showed parietal overlap of cortical activation patterns from the four cognitive domains. The authors then applied fiber tracking to diffusion tensor images to determine that parietal activation patterns across all four domains connected to a small region of subcortical parietal white matter at a location congruent with the subangular gyrus lesion in a reported case of pure Gerstmann syndrome.[3]

The authors postulate that Gerstmann's triad of symptoms arises from intraparietal disconnection after damage to a focal region of subcortical white matter.

■ **COMMENTARY**

Gerstmann thought the syndrome he described was a disorder of the body schema restricted to the hand and fingers. Detailed neuropsychological testing in a patient with pure Gerstmann syndrome indicates that the impairment is attributable to disorders of a spatial nature.[3] Mayer and colleagues studied their patient with MRI and cognitive testing. MRI showed a focal ischemic lesion located subcortically in the inferior part of the left angular gyrus and involving callosal fibers. The cortical layers were spared. Cognitive testing excluded language, praxis, memory, and intelligence disorders. The Gerstmann tetrad was associated with impaired ability to perform tasks necessitating mental rotation. On the basis of the report of Mayer and associates, it seems legitimate to consider the Gerstmann tetrad a true syndrome.

The report of Rusconi and colleagues supports the prevailing view that the cognitive functions impaired in Gerstmann syndrome do not share a common neuronal network and that their occurrence in cases of parietal lobe injury is due to anatomical proximity. The fiber tracts subserving the Gerstmann tetrad of cognitive functions are separate but co-localized in the subcortical white matter of the parietal lobe. Therefore, a purely subcortical lesion could produce the "cortical" deficits of Gerstmann syndrome by disconnection. A classical disconnection syndrome of alexia without agraphia has been reported in a patient with multiple sclerosis.[4]

(If Neurology Alert *readers have seen cases of multiple sclerosis with Gerstmann syndrome, the editors would like to hear about it. Contact information is listed on page 34.)*

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1. Critchley M. The enigma of Gerstmann's syndrome. *Brain* 1966;89:183-198.
2. Roux FE, et al. Writing, calculating, and finger recognition in the region of the angular gyrus: A cortical stimulation study of Gerstmann syndrome. *J Neurosurg* 2003;99:716-727.
3. Mayer E, et al. A pure case of Gerstmann syndrome with a subangular lesion. *Brain* 1999;122:1007-1020.
4. Dogulu CF, et al. Alexia without agraphia in multiple sclerosis. *J Neurol Neurosurg Psy* 1996;61:528. ■

How to Differentiate Between Organic and Psychogenic Spinal Myoclonus

ABSTRACT & COMMENTARY

By Panida Piboolnurak, MD

Assistant Professor, Department of Neurology and Neuroscience, Weill Medical College, Cornell University

Dr. Piboolnurak reports no financial relationship relevant to this field of study.

Synopsis: *Detection of Bereitschaftspotential (BP) via EEG-EMG back averaging is helpful in differentiating psychogenic myoclonus from organic myoclonus. But, technical limitations of this technique and its availability have limited its utilization in clinical practice.*

Sources: Esposito M., et al. Idiopathic Spinal Myoclonus: A Clinical and Neurophysiological Assessment of a Movement Disorder of Uncertain Origin. *Mov Disord* Nov. 11, 2009. (www.interscience. wiley.com). DOI: 10.1002/mds.22812.

MYOCLONUS IS A MOVEMENT DISORDER DESCRIBED AS brief, shock-like movements caused by muscle contraction or inhibition of ongoing muscle activity. It may originate from the central or peripheral nervous system. Spinal myoclonus originates from the spinal cord and can be subdivided into spinal segmental myoclonus and propriospinal myoclonus. In spinal segmental myoclonus, myoclonus is limited to muscles innervated by one or two contiguous spinal segments. Propriospinal myoclonus is characterized by axial muscle contractions as a result of a spinal myoclonic generator recruiting axial muscles up and down the spinal cord via propriospinal pathways. Although spinal cord lesions can be seen in patients with spinal myoclonus, structural lesions may not be present in some patients. Distinguishing myoclonus of organic origin from psychogenic myoclonus can also be difficult. Detection of a

Bereitschaftspotential (BP) by EEG-EMG back averaging analysis can be helpful in differentiating between these two etiologies. BP consisted of early BP and late BP. The early BP starts two seconds and late BP starts about 400 milliseconds before the onset of a voluntary jerk.

In this study, the authors looked clinically and electrophysiologically at a series of 20 patients with idiopathic spinal myoclonus. EMG showed a pattern consistent with spinal segmental myoclonus in four patients and with propriospinal myoclonus in 16 patients. Seven patients showed a consistent pattern of muscle propagation, but 13 patients did not show a consistent pattern. A definite BP was detected in six patients and possible BP was detected in nine patients. BP was absent in five patients. Clinically, organic myoclonus was considered in five patients and psychogenic myoclonus was considered in 10 patients. In the remaining five patients, two clinicians had different opinions on the diagnosis. In the clinically diagnosed organic myoclonus group (n = 5), definite BP was detected in four cases and possible BP was detected in one case. In the clinically diagnosed psychogenic myoclonus group (n = 10), there was one case with definite BP, six cases with possible BP, and three cases with absent BP. In five patients with unclear clinical diagnosis, one case had definite BP, two cases had possible BP, and two cases had no BP.

The authors concluded that although BP detection is a useful tool, it has limitations because it may not be possible to reach a definite conclusion as to whether a BP is present or not. Moreover, if the jerking movements are too frequent (> 1 every 5 seconds), a BP may not be able to be recorded even if the movements are performed voluntarily. It is also difficult to assess for BP if the movements are very infrequent. In addition, head movements can create movement artifacts in the EEG recording.

■ COMMENTARY

It can be difficult to distinguish between psychogenic and organic myoclonus based on neurological examination and EMG pattern (burst length and pattern of muscle activation). Since BP precedes a voluntary jerk, the presence of BP would suggest myoclonus of psychogenic origin. However, it has technical limitations and there is no standardization of techniques to record BP. Moreover, there are only a few institutions that can perform EEG-EMG back averaging analysis. For these reasons, diagnosis of organic or psychogenic myoclonus still relies on careful history and neurological examination. ■

When Does Acute Guillain-Barré Presage Chronic Inflammatory Demyelinating Polyneuropathy?

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Acute-onset CIDP is difficult to diagnose and distinguish from GBS. It should be suspected when there are prominent sensory signs at onset of the illness.*

Source: Dionne A, et al. Clinical and electrophysiological parameters that distinguish acute-onset chronic inflammatory demyelinating polyneuropathy from acute inflammatory demyelinating polyneuropathy. *Muscle Nerve* 2009: (www.interscience. wiley.com). DOI 10.1002/mus.21480.

CAN THE ACUTE PRESENTATION OF CHRONIC INFLAMMAtory demyelinating polyneuropathy (CIDP), which occurs in 16% of CIDP patients, be distinguished from Guillain-Barré syndrome (GBS), early in the course? Currently, two months of progression is mandated to consider a diagnosis of CIDP. Early differentiation would have obvious therapeutic and prognostic implications. To answer this question, a retrospective chart review of the clinical and electrodiagnostic record was undertaken of all patients with GBS and acute-onset CIDP (A-CIDP) seen between 1993 and 2007 at the London Health Sciences Center, London, Ontario, Canada, and examined by the senior author. GBS was diagnosed using the Asbury criteria and required muscle weakness with areflexia or hyporeflexia, reached a plateau in less than four weeks, and was confirmed at follow up with no relapse, no progression beyond eight weeks, and no need for ongoing treatment. GBS variants, including Miller-Fisher syndrome, regional variants, and axonal GBS were excluded, as were those with other possible etiologies, including hereditary neuropathy, diabetes, paraproteinemia, and neoplasm. A-CIDP diagnosis required an acute presentation over four weeks initially diagnosed as GBS, but which progressed

beyond eight weeks, relapsed, or required continued therapy, including intravenous immunoglobulin, plasmapheresis, or immunosuppressive therapy. Motor and sensory nerve conduction studies were performed using standard technique and only the initial studies obtained within four weeks were analyzed. Criteria for diagnosing conduction block, temporal dispersion, slowed conduction velocity, and prolonged distal and F-wave latencies were those established by the Inflammatory Neuropathy Cause and Treatment Group (*Ann Neurol* 2001;50;195-201). Statistical analysis comprised Fisher's exact test and the unpaired t-test, with $P<0.05$ considered statistically significant.

Among 20 CIDP and 50 GBS patients screened over the study period, 15 CIDP and 30 GBS patients, respectively, satisfied inclusion criteria. Mean age at onset was 43 and 48 years, respectively, with no significant difference between groups for age or gender. Prominent sensory signs were more likely, and autonomic dysfunction, facial weakness, antecedent infectious illness, and assisted mechanical ventilation were less likely, in A-CIDP compared to GBS. Sensory signs included sensory ataxia, and stocking-glove distribution impairment of vibration and pinprick sensation. Sensory symptoms, back or radicular pain, and electrodiagnostic findings were not significantly different between the two groups. Consideration of the aforementioned early clinical features is worthwhile, as they may presage development of CIDP in a patient who otherwise resembles GBS.

■ COMMENTARY

Which treatments are available for chronic inflammatory demyelinating polyneuropathy? Up to 65%–95% respond to steroids. Some predominantly motor CIDP patients may worsen but this resolves after steroid withdrawal. Intravenous immunoglobulin (IVIG) provides both short- and long-term benefit, with 54% immediately responding and 34% maintaining stability with continued infusions. Plasma exchange (PE) is beneficial, but relapse rate after PE withdrawal, and the effects of continued maintenance therapy, remains unreported. No significant difference in efficacy has been demonstrated between steroids, IVIG, or PE, but cost and side-effect profiles differ significantly. In a recent report, methotrexate demonstrated no reduction in the need for ongoing steroid or IVIG. Uncontrolled studies suggest azathioprine may be beneficial, as well as interferon-beta, but in the single reported randomized controlled trial, the latter was of no benefit. Cyclosporin and cyclophosphamide are probably beneficial but the latter carries substantial toxicity. Mycophenolate mofetil, less toxic and reportedly beneficial in uncontrolled studies; and tacrolimus, etanercept, and stem-cell transplants are other potential therapies that await testing in randomized controlled trials. ■

Therapeutic Hypothermia for Neonatal Hypoxic–Ischemic Encephalopathy: Do Lesions on MRI Predict Outcome?

ABSTRACT & COMMENTARY

By Toshiki Takenouchi, MD, and Steven Weinstein, MD

Dr. Takenouchi is Clinical Fellow in Neonatal Neurology, and Dr. Weinstein is Director of the Pediatric Comprehensive Epilepsy Program, Weill Cornell Medical School, New York Presbyterian Hospital.

Neither Dr. Takenouchi nor Dr. Weinstein report any financial relationships relevant to this field of study.

Synopsis: *MRI analysis of a subset of infants from the Total Body Hypothermia for Neonatal Encephalopathy (TOBY) trial showed that total body hypothermia decreases brain tissue injury in infants with hypoxic-ischemic encephalopathy (HIE).*

Source: Rutherford M, et.al. Assessment of brain tissue injury after moderate hypothermia in neonates with hypoxic-ischaemic encephalopathy: A nested substudy of a randomised controlled trial. *Lancet Neurol*, online November 6, 2009. DOI:10.1016/S1474-4422(09)70295-70299.

TOBY WAS A EUROPEAN, MULTICENTER, RANDOMIZED, controlled clinical trial conducted between 2002 and 2006 to evaluate the efficacy of total body hypothermia to treat neonatal hypoxic-ischemic encephalopathy (HIE) in infants ≥ 36 weeks gestation. Infants with moderate to severe encephalopathy were randomized, at < 6 hours of age, to either total body hypothermia at 33.5°C for 72 hours (n=163) or normothermic intensive care (n=162). At 18 months, there was no significant reduction in the combined rate of death or severe disability, but there was better neurologic outcome in survivors.

In the current subset analysis, the authors analyzed the MRIs of 131 infants recruited from the original TOBY study (n=325). The amplitude of integrated EEG, an objective measure of encephalopathy, was similar in each group. MRI was obtained in a subset of early survivors, representing 40% of the original subjects, but selection

criteria for imaging was not provided. The median time of postnatal scans was eight days, ranging from two to 30 days. 37 of 59 (63%) infants scanned at less than eight days of age had major abnormalities on MRI that were predictive of poor outcome, compared to 34 of 72 (47%) of infants scanned after eight days (p=0.08).

Two independent radiologists, blinded to the outcomes, reviewed T1- and T2-weighted MR images and counted lesions in the basal ganglia, thalami, posterior limb of the internal capsule, subcortical white matter, and cortex as well as identifying intracranial hemorrhages and sinus thrombosis. Therapeutic hypothermia was associated with a reduction in lesions in the basal ganglia or thalamus (OR=0.36, 95% CI 0.15-0.84; p=0.02), subcortical white matter (OR=0.30, 0.12-0.77; p=0.01), and posterior limb of the internal capsule (OR=0.38, 0.17-0o85; p=0.02). Compared with the control group, infants treated with hypothermia had fewer scans that were predictive of later neurological abnormalities (OR=0.41, 0.20-0.92; p=0.03) and were more likely to have normal scans (OR=2.81, 1.13-6.93; p=0.03). The predictive accuracy of moderate or severe lesions in the basal ganglia and thalami, severe white-matter lesions, or an abnormal posterior limb of the internal capsule, for death or severe disability at 18 months of age was 0.84 (95% CI 0.74-0.94) in the cooled group and 0.81 (0.71-0.91) in the non-cooled group.

■ COMMENTARY

Moderate to severe neonatal HIE is a serious complication of pregnancy and delivery, since it is associated with a high incidence of neurological impairment. Since 2005, several large, international, multicenter, randomized control trials have shown marginal benefits of therapeutic hypothermia for term infants with moderate to severe HIE, especially for short-term neurologic outcome.[1] Although therapeutic hypothermia has become widely available and is considered a standard of care for neonatal HIE, the optimal temperature and duration of treatment remain to be determined.

Brain MRI has become a standard to objectively assess anatomical changes from the ischemic insult and is highly predictive of outcome in this population. However, the predictive value of MRI in infants undergoing therapeutic hypothermia needs to be validated. The current study retrospectively analyzed a large number of MRIs in infants treated with hypothermia using an objective scoring system and demonstrated that hypothermia decreases cerebral lesions seen on MRI, consistent with a similar, but smaller report by Rutherford in 2005.[2]

There are technical limitations of this study that warrant caution in interpretation. First, the authors had to combine MRI data sets from scanners of different manufacturers, with different magnetic field strengths, and different acquisition parameters. Second, the investigators only utilized T1- and T2-weighted images and did not include diffusion weighted imaging (DWI). DWI has been considered the most sensitive method to identify acute ischemic injury with MRI and has been widely utilized in the neonatal population. Third, each MRI was obtained at the discretion of the treating physician and the acquisition of MRI ranged from two to 30 days with the median of eight days. Therefore, it is not possible to determine the best timing, acquisition sequences, or parameters of scanning from this study.

References

1. Azzopardi DV, et al. Moderate hypothermia to treat perinatal asphyxial encephalopathy. *N Engl J Med* 2009;361:1349-1358.
2. Rutherford MA, et al. Mild hypothermia and the distribution of cerebral lesions in neonates with hypoxic-ischemic encephalopathy. *Pediatrics* 2005;116:1001-1006. ■

CME Objectives

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

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

CME Questions

23. REM sleep behavior disorder is associated with several neurodegenerative disorders, including Parkinson disease.

a. True
b. False

24. The Gerstmann syndrome has been noted following left hemisphere lesions at all of these locations except:

a. parietal cortex
b. angular gyrus and subangular white matter
c. subangular white matter and the corpus collosum
d. angular gyrus only
e. subcortical white matter of parietal lobe

25. Which statement concerning Bereitschaftspotential (BP) is incorrect?

a. BP is present when the movement is voluntary.
b. BP can be detected by a routine EEG recording.
c. Early BP starts about 2 seconds before the onset of jerking movement.

d. It is difficult to assess for BP if the movements are too frequent or very infrequent.

26. Compared to Guillain-Barré syndrome, in acute-onset chronic inflammatory demyelinating polyneuropathy (CIDP):
a. Prominent sensory signs are more likely,
b. Autonomic dysfunction is less likely
c. Facial weakness is less likely
d. Antecedent infectious illness is less likely
e. All the above are true

27. All of the following are true regarding neonatal hypoxic-ischemic encephalopathy EXCEPT:
a. Therapeutic hypothermia improves neurological outcome.
b. MRI abnormalities can predict neurological impairment.
c. Early MRI can predict good or poor neurological outcome.
d. Lesions in the basal ganglia or thalamus predict poor neurological outcomes.

28. Alteplase, given intravenously for acute brain infarction, is associated with an increased risk of intracerebral hemorrhage as the time from onset of symptoms is extended.
a. True
b. False

29. Chagas Disease is a risk factor for ischemic stroke in patients born and reared in South America.
a. True
b. False/

Answers: 23. a; 24.D, 25. b, 26. e, 27. c, 28. b, 29. a

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*

Editor's note: *Stroke is one of the topics most requested by* Neurology Alert *readers. With this issue,* we *begin a new feature that gives you a concise review of the most recent literature on stroke.*

Intravenous Thrombolysis Time-window Can Be Extended to 4.5 Hours

In a follow-up subgroup analysis to their landmark report (*N Engl J Med* 2008:359;1317-1329), the ECASS III investigators have given us more robust evidence to support extending the window for treatment of patients with acute ischemic stroke using intravenous alteplase (rTPA). After giving the standard dose (0.9 mg/kg bodyweight with a maximum of 90 mg, over one hour) of intravenous rTPA, the investigators showed a statistically significant improvement in the treated group v. placebo in functional endpoints at day 30 and day 90 (mRS 0-1, mRS 0-2, Barthel index > 85, and global outcome statistic), and treatment response (8-point improvement or 0-1 score on the NIH stroke scale).

Although not reaching statistical significance, additional end-points all showed a clear trend in favor of rTPA, including older patients (<65 years: OR=1.61 and >65 years; OR= 1.15), and the effectiveness was independent of the severity of stroke—all groups showed benefit. The incidence of symptomatic intracranial hemorrhage, the most feared complication, seemed to be independent of previous antiplatelet drug use and time of onset of symptoms to treatment, but was higher in older age groups (<65 years: OR=0.74, >65 years: OR=5.79. It is notable that the upper limit of age for patient enrollment in this study was 80 years.

Based on the ECASS III reports, stroke teams in the U.S. should consider extending the time window of administration of intravenous rTPA to 4.5 hours, but should take special care in using informed consent, since this extension is not yet approved by the FDA.

Bluhmki E, et al. Stroke treatment with alteplase given 3.0 - 4.5 h after onset of acute ischemic stroke (ECASS III): Additional outcomes and subgroup analysis of a randomized controlled trial. *Lancet Neurology* 2009:8:1095-1102. ■

Niacin Added to a Statin Increases HDL and Reduces Carotid Atherosclerosis

Neurologists who are caring for stroke patients are becoming more involved in secondary prevention efforts in addition to primary care physicians. This study, from Walter Reed Army Medical Center, provides guidance on the most effective drug combination to lower LDL cholesterol, raise HDL cholesterol, and in the end, hopefully reduce carotid atherosclerosis. The authors enrolled patients at high-risk for coronary artery disease who were receiving long-term statin therapy, with LDL cholesterol under 100 mg/dl and HDL cholesterol under 50 mg/dl for men and under 55 mg/dl for women, and randomized them to receive extended-dose niacin (target=2000 mg/day) or ezetimibe (10 mg /day). The primary end-point was change in mean common carotid intima-media thickness after 14 months.

Mean HDL level increased in the niacin group by 18.4% to 50 mg/dl and mean LDL decreased in the ezetimibe group by 19.2% to 66 mg/dl. Niacin therapy also reduced LDL and triglyceride levels, and ezetimibe reduced HDL and triglyceride. Compared to ezetimibe, niacin had greater efficacy in reducing both mean and maximum carotid intima-media thickness. Paradoxically, greater reductions in LDL in the ezetimibe group

were associated with an increase in carotid intima-media thickness. The incidence of major cardiovascular events was lower in the niacin group (1% v. 5%, p=0.04).

Based on this study, we would recommend the addition of slow-release niacin to a statin, in patients who would benefit from a lower LDL, or a higher HDL.

Taylor AJ, et al. Extended-release niacin or ezetimibe and carotid intima-media thickness. *N Engl J Med* 2009:361: 2113-2122. ■

Chagas Disease Is a Risk Factor for Stroke

CHAGAS DISEASE (CD), OR AMERICAN TRYPANOsomiasis, is a common protozoan infection and public health problem in South America, and is a leading cause of cardiomyopathy. It is estimated that it may affect up to 18 million people in South America, and can be acquired as a child but not show any manifestations until late in life, presenting with heart failure and cardiac arrhythmias. Because of extensive immigration and international travel, the U.S. FDA recently approved the first screening test for CD among blood donors. Older autopsy studies have shown a high rate of cerebral infarctions in patients who have died from CD, and now a Brazilian group has done a case-control study to look at the prevalence of CD is Brazilian patients who presented with acute cerebral infarction. In comparing 101 consecutive stroke patients with 100 acute coronary syndrome patients who all had similar cardiovascular risk factors, these investigators found that CD-positive serology was an independent risk factor for stroke (OR=7.17;95%CI,1.50-34.19). The mechanism is uncertain, but may be due to cardiomyopathy, undiagnosed atrial fibrillation, or other inflammatory endothelial disorders. It is recommended that patients with acute stroke whose country of origin is in South America, have blood testing for CD.

Paixão LC, et al. Chagas disease: Independent risk factor for stroke. *Stroke* 2009;40:3691-3694. ■

"TIAs" May Be Caused by Focal Cortical Subarachnoid Hemorrhage

THE AUTHORS, FROM SUNNYBROOK HEALTH SCIENCES Center in Toronto, report 4 patients, all elderly (68-85 years), who presented with recurrent episodes of unilateral paresthesias beginning in the face or arm, and spreading over the contiguous body regions at a speed similar to migraine aura (about 20 minutes) and followed by unilateral headache. The time course of symptoms was consistent with the phenomenon of "speading cortical depression." Brain imaging with CT and MRI revealed a small focus of subarachnoid hemorrhage (SAH) in a cortical sulcus in the hemisphere contralateral to the sensory symptoms. The focus of SAH was clearly seen on gradient-echo MRI, and cerebral angiography did not show any vascular lesions to explain the SAH. The authors speculate that these patients probably have cerebral amyloid angiopathy (CAA) as a cause for the focal, spontaneous SAH. Focal, cortical SAH has been shown to induce "speading cortical depression" and other investigators have reported similar cases in patients with CAA. Pathologically, the meningeal vessels are heavily infiltrated with amyloid and the subarachnoid space is often the place where cerebral hemorrhage begins in these patients. Antiepileptic medications had a variable benefit in preventing the episodes, but in all cases, the spells stopped after several months.

Izenberg A, et.al. Crescendo transient aura attacks: A transient ischemic attack mimic caused by focal subarachnoid hemorrhage. *Stroke* 2009;40:3725-3729. ■

Phenytoin Use May Worsen Outcome after Intracerebral Hemorrhage

THERE IS CONSIDERABLE DEBATE OVER THE USE OF PROphylactic antiepileptic medications (AED) in patients with subarachnoid hemorrhage (SAH) and intracerebral hemorrhage (ICH). Recently, large survey series have indicated that overall functional outcome and mortality may be worse in patients with SAH who are prophylactically treated with phenytoin, and guidelines now recommend AED use for only a few days after the acute episode. In this prospective, observational study from Northwestern University in Chicago, 98 patients with ICH were followed, free-phenytoin levels were measured, and patients with depressed consciousness were monitored with continuous electroencephalography (EEG). Seven patients had a clinical seizure—five on the day of the ICH. Phenytoin use was associated with more fever, worse NIH stroke scale and modified Rankin at 14 days, and an increased risk of poor outcome at three months. Levetiracetam, a newer medication with limited use, could not be assessed in this study.

Naidech AM, et al. Anticonvulsant use and outcomes after intracerebral hemorrhage. *Stroke* 2009;40:3810-3815. ■

In Future Issues: **Treatment of Guillain-Barré Syndrome**

Dear *Neurology Alert* Subscriber:

This issue of your newsletter marks the start of a new continuing medical education (CME) or continuing nursing education (CNE) semester and provides us with an opportunity to review the procedures.

Neurology Alert, sponsored by AHC Media LLC, provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours — the best possible patient care.

The objectives of *Neurology Alert* are to help participants:

a.) Present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;
b.) Discuss the pathogenesis and treatment of pain;
c.) Present basic science lessons in brain function;
d.) Discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs;
e.) Discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness.

Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers against the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

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Cynthia Molnar
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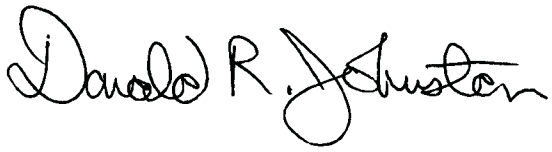

Donald R. Johnston
Senior Vice President/Group Publisher
AHC Media LLC

N #4005

3525 Piedmont Road NE
Building Six, Suite 400
Atlanta, Georgia 30305-1515
Tel (404) 262-7436
Fax (404) 262-7837
www.ahcmedia.com

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The relationship of FPG and A1c to diabetic retinopathy

Source: Cheng YJ, et al. Association of A1C and fasting plasma glucose levels with diabetic retinopathy prevalence in the U.S. population. *Diabetes Care* 2009;32:2027-2032.

THE IDEA THAT A1c MIGHT BE A REASONABLE metric to make the diagnosis of diabetes has been kicking around for more than a decade. Only very recently has there been advocacy from the ADA that A1c may be an acceptable method for diagnosis of diabetes (A1c ≥ 6.2%); a primary reason for this shift in perception is the widespread adoption of a nationally standardized A1c testing method. Ultimately, diagnosis is intended to go beyond simply categorizing an individual as diabetic or non-diabetic; rather, it is intended to predict risk for important complications of diabetes like retinopathy.

The NHANES (National Health and Nutrition Examination Survey) is a cross-sectional sampling of non-institutionalized civilian adults. From the NHANES 2005-2006 study population, a group of adults age ≥ 40 years had assessment of retinopathy, A1c, and fasting plasma glucose (FPG).

There was a steep increase in frequency of retinopathy at an A1c ≥ 5.5%. Although a similar increased risk was seen at a FPG of 126 mg/dL, overall, the A1c was a better predictor than FPG. Since A1c may be obtained whether or not the subject has fasted, it may become a more convenient (as well as more sensitive) method than FPG for identifying risk of retinopathy. ■

Getting the most bang for your buck with lipid measurement

Source: The Emerging Risk Factors Collaboration. Major lipids, apolipoproteins, and risk of vascular disease. *JAMA* 2009;302:1993-2000.

THE EMERGING RISK FACTORS COLLABORATION collected data from prospective observational studies of persons without CV disease at baseline (n = 69 studies, with 302,430 participants). Lipid fractions measured in these studies included LDL, HDL, apo B, and apo A1. Risk for incurring CV endpoints was stratified for each lipid fraction.

Triglycerides have always been the lipid fraction demonstrating the weakest association to CVD endpoints. In this data set, although the unadjusted hazard ratio for triglycerides demonstrated increased hazard, adjusted hazard ratios were not convincing. In contrast, subjects with the lowest HDL levels showed an almost 3-fold greater hazard ratio for CV events than those in the highest third. The ratio of apo B:apo A1 was also an important CV risk predictor.

Interestingly, measurement of total cholesterol, HDL, apo B, and apo A1 in the non-fasting state did not appear to appreciably alter their predictive value. Sufficient information for risk prediction, according to these data, is obtained by simply measuring cholesterol levels (total and HDL). Additionally, the authors were not able to identify any significant additional CV risk prediction by adding triglyceride levels to their calculations.

The simplicity of focusing upon total and HDL cholesterol, and being able to use non-fasting results, may enable clinicians to more readily gather predictive information on a wider population of patients. ■

Nortriptyline, gabapentin, or both for neuropathic pain

Source: Gilron I, et al. Nortriptyline and gabapentin, alone and in combination for neuropathic pain: A double-blind, randomised controlled crossover trial. *Lancet* 2009;374:1252-1261.

NEUROPATHIC PAIN (NPN), SUCH AS post-herpetic neuralgia or diabetic peripheral neuropathic pain, often requires what has been described as rational polypharmacy: the combination of multiple agents in an attempt to gain maximum therapeutic advantage while minimizing adverse effects. Both nortriptyline and gabapentin have achieved some success in modulation of NPN as monotherapy. Since the mechanism of action of these agents is complementary, a trial of their combination has intellectual appeal. When choosing among antidepressants for analgesic effects, norepinephrine re-uptake inhibition appears to be a critical component. Hence, SSRIs have minimal effect, but tricyclics (e.g, amitriptyline, nortriptyline), SNRIs (e.g., duloxetine, venlafaxine), and highly selective norepinephrine re-uptake inhibitors (e.g., milnacipran) effectively reduce pain.

Combination nortriptyline and gabapentin provided significantly greater pain reduction than either agent alone. No serious adverse effects were seen in either mono- or combination therapy. Clinicians are already commonly applying combination therapies to neuropathic pain syndromes; it is gratifying to encounter sound evidence supporting this practice. ■

Which insulin regimen for type 2 diabetes

Source: Holman RR, et al. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N Engl J Med* 2009; 361:1736-1747.

THE MOST RECENTLY PUBLISHED ADA/EASD consensus algorithm for management of type 2 diabetes (DM2) suggests that when the combination of metformin and lifestyle is insufficient to control diabetes, either sulfonylurea (if close to goal) or insulin is the most well-validated next step. Because there are many different insulins to choose from, the clinician may be uncertain whether basal insulin (i.e., detemir, glargine, NPH), prandial insulin (i.e., regular insulin or rapid-acting insulin analog), or biphasic insulin (a combination containing a basal as well as prandial insulin) should be preferred.

Holman et al performed a 3-year trial in DM2 subjects (n = 708) not at A1c goal with the combination of metformin and a sulfonylurea. Subjects were randomized to biphasic insulin aspart (BIA) bid, prandial insulin aspart (PIA) tid, or insulin detemir (DET) qd (some received detemir bid).

At 3 years, there was no statistically significant between-group difference in A1c attained. Hypoglycemia was least frequent in the DET group, and most common in the PIA cohort. Weight gain was least in the DET group, and greatest in the PIA group.

All regimens were successful in attaining goal A1c. Because hypoglycemia and/or weight gain are often deal breakers for our patients, basal insulin regimens may be preferred. ■

Cardioprotective effects of ACE inhibitors in African American men

Source: Papademetriou V, et al. Protective effects of angiotensin-converting enzyme inhibitors in high-risk African American men with coronary heart disease. *J Clin Hypertens* 2009;11: 621-626.

THE HOPE TRIAL CONVINCED MANY experts that midlife adults (age ≥ 55 years) with existing vasculopathy (history of CAD, CVD, diabetes and CV risk factors) will have improved outcomes on an ACE inhibitor (ramipril, to be specific). There is controversy about whether African Americans achieve similar risk reduction as other ethnicities; for instance, in the SOLVD CHF trial, retrospective analysis suggested less benefit for some endpoints in African Americans.

Papademetriou reviewed electronic records from the Washington, DC, VA Medical Center to study African American study subjects who had CAD documented by catheterization (n = 810). Subjects were parsed into those who had vs had not been treated with an ACE inhibitor.

Over a study period of 3-10 years (mean, 6.8 years), the relative risk reduction for CAD mortality was more than 30% in those treated with ACE inhibitors. All-cause mortality was 80% higher in African American patients who had *not* been treated with ACE inhibitors. Because many African American patients have relatively low renin levels, some clinicians have doubted whether CV benefits would be readily achieved with ACE inhibitors. This data analysis suggests substantial benefit from ACE inhibitor treatment in African Americans with CAD. ■

Missed opportunity: Aldosterone antagonists in heart failure

Source: Albert NM, et al. Use of aldosterone antagonists in heart failure. *JAMA* 2009;302:1658-1665.

THE SEMINAL RALES TRIAL (RANDOMized Aldactone Evaluation Study), in which patients with NYHA Class III-IV systolic heart failure received either aldactone or placebo in addition to standard-of-care treatment (e.g., ACE inhibitors, beta blockers, digoxin) indicated that the utilization of this well tolerated, inexpensive treatment could reduce mortality by as much as 30%.

One might anticipate that such benefits would result in widespread utilization of aldosterone antagonists in heart failure.

Albert et al reviewed data from more than 200 U.S. hospitals, encompassing 43,625 patient admissions for heart failure over the 2005-2007 time period. By this time, the RALES data were more than 5 years old. Contraindications to this life-saving treatment are few, with hyperkalemia being the most common.

According to their analysis, less than 33% of patients with heart failure who were eligible for treatment with an aldosterone antagonist (i.e., without contraindications) received one. With proper monitoring, aldosterone antagonist therapy reduces risk, is safe, and is well tolerated. Although aldosterone antagonist use improved over time (from a baseline rate of 28% to an end-of-study rate of 34%), much opportunity of reduction of mortality was missed. ■

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Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: paula.cousins@ahcmedia.com
World Wide Web: www.ahcmedia.com
Address Correspondence to: AHC Media LLC
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Niacin Beats Ezetimibe Head to Head

In this issue: *Statin and niacin increase HDL-C, omeprazole reduces effectiveness of clopidogrel, darbepoetin increases risk of stroke, statins decrease risk of gallstone disease, FDA Actions.*

Statin plus niacin or ezetimibe?

Raising HDL-cholesterol (HDL-C) with niacin plus a statin is superior to lowering LDL-cholesterol (LDL-C) with ezetimibe plus statin in reversing atherosclerosis according to the widely reported ARBITER trial published on-line in the *New England Journal of Medicine* in November and simultaneously reported at the American Heart Association meeting in Orlando, FL. The trial enrolled more than 200 patients with coronary heart disease or a coronary heart disease equivalent who were receiving long-term statin therapy with an LDL-C < 100 mg/dL along with an HDL-C < 50 mg/dL for men or 55 mg/dL for women. The patients were randomly assigned to receive extended-release niacin (target is 2000 mg/day) or ezetimibe (10 mg/day). The primary endpoint was the difference in change from baseline in mean and maximal carotid intima-media thickness after 14 months. The trial was terminated early in July of 2009. Both drugs were effective in their roles — the mean HDL-C in the niacin group increased by 18.4% over the 14-month study period ($P < 0.001$) and the mean LDL-C level in the ezetimibe group decreased by 19.2% ($P < 0.001$). Niacin significantly reduced LDL-C and triglycerides as well, while ezetimibe lead to a reduction in HDL-C and triglycerides. Niacin was superior to ezetimibe in reducing the primary endpoint, leading to a reduction of both mean ($P = 0.001$) and maximal carotid intima-media thickness ($P \leq 0.001$ for all comparisons). Paradoxically, greater reductions in LDL-C seen with ezetimibe were significantly associated with increases in the carotid intima-media thickness. The incidence of major cardiovascular events was also lower in the niacin group than in the ezetimibe group (1% vs 5%; $P = 0.04$ by the chi square test) (published on-line at: www.nejm.org; Nov. 15, 2009).

The study has received enormous attention not only because of the primary endpoint, but also because of the significant reduction in major adverse cardiac events in the niacin group, even though the numbers were quite small. At least one editorialist laments the early termination of the study and feels that it is impossible to make recommendations regarding the "adjuvant agent of choice" based on the small numbers (The HALTS Trial — Halting Atherosclerosis or Halted Too Early; published on-line at: www.nejm.org; Nov. 15, 2009). Still, this study provides enough evidence to consider adding niacin to a statin in patients who are at risk of or have low HDL-C. It also deals another blow to ezetimibe (Zetia®) and its partner drug ezetimibe/simvastatin (Vytorin®).

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) 262-5468. E-mail: paula.cousins@ahcmedia.com.

Omeprazole's effect on clopidogrel

The FDA has issued a warning regarding the combination of clopidogrel (Plavix®) with omeprazole (Prilosec®) citing new data that suggest that the combination reduces clopidogrel's effectiveness by about half. Studies reported in 2009 suggested that omeprazole may block clopidogrel's conversion to its active metabolite via CYP2C19, an enzyme that is inhibited by omeprazole. New studies requested by the FDA from the manufacturers confirm a significant interaction between the two drugs, which can significantly hinder clopidogrel's ability to prevent platelet aggregation in patients at risk for heart disease. Omeprazole and clopidogrel are commonly prescribed together to prevent GI bleeding. At this time it is unclear whether this interaction extends to other proton pump inhibitors, although physicians are encouraged to avoid a combination of clopidogrel with esomeprazole (Nexium®, cimetidine (Tagamet®), and other drugs known to inhibit CYP2C19. The FDA is recommending that patients who need GI protection in conjunction with clopidogrel may safely use ranitidine (Zantac®), famotidine (Pepcid®), nizatidine (Axid®), or oral antacids.

Darbepoetin and risk of stroke

Darbepoetin alfa (Aranesp®) is commonly used in patients with chronic kidney disease and diabetes for the treatment of anemia. A new study suggests that the drug may be associated with increased risk of stroke in this patient population. More than 4000 patients with diabetes, chronic kidney disease, and anemia were randomly assigned to darbepoetin alfa to achieve a hemoglobin level of 13 g/dL or placebo with rescue darbepoetin alfa if hemoglobin levels dropped < 9 g/dL. The primary endpoints were the composite outcomes of death or cardiovascular event, and death or end-stage renal disease. After a follow up of 2.5 years, darbepoetin alfa was ineffective at preventing either primary outcome, and, more importantly, the rate of fatal or nonfatal stroke occurred almost twice as often in the treatment group (101 patients assigned to darbepoetin alfa vs 53 patients assigned to placebo; HR, 1.92; 95% confidence interval, 1.38-2.68; $P < 0.001$). The authors conclude that the use of darbepoetin alfa in patients with diabetes, chronic kidney disease, and moderate anemia who are not undergoing dialysis did not reduce the outcome of death, cardiovascular events, or renal events, but was associated with increased risk of stroke. For many "this risk will outweigh the potential benefits" of the drug (*N Engl J Med* 2009;361:2019-2032). Erythropoiesis-stimulating agents have come under fire in the treatment of cancer-associated anemia, and now in renal patients as well. As pointed out in an accompanying editorial, the risks and benefits of these agents must be weighed, namely an increased risk of stroke vs a perceived improvement in quality of life (*N Engl J Med* 2009; 361:2089-2090).

Statins and gallstone disease

Statins have been shown to reduce the risk of cardiovascular disease and death from all causes. Now another potential benefit is being reported: Statins may reduce gallstone disease. Utilizing a large patient database from the United Kingdom, researchers looked at the risk of developing gallstones followed by cholecystectomy in relation to exposure to lipid-lowering agents. The longer patients took statins, the lower the risk for gallstone disease, with patients who had filled 20 or more prescriptions noticing 36% reduction in risk (AOR, 0.64; 95% confidence interval, 0.59-0.70). The authors conclude that long-term use of statins is associated with a decrease risk of gallstones followed by cholecystectomy (*JAMA* 2009;302:2001-2007).

FDA Actions

The FDA has approved a new topical treatment for the treatment of post-herpetic neuralgia (PHN). The capsaicin 8% patch must be applied to the skin by a health care professional since placement may be quite painful, requiring the use of a local topical anesthetic. The patch is applied for one hour during which patients must be monitored, including observation for increases in blood pressure. The patches may be cut to conform to the area of pain and up to 4 patches may be used. The one-hour application is reported to provide up to 12 weeks of reduced pain from PHN. The capsaicin 8% patch will be manufactured by Lohmann Therapie-Systems and distributed by NeurogesX as Qutenza™.

The FDA has approved romidepsin for the treatment of cutaneous T-cell lymphoma in patients who received at least one prior systemic therapy. The drug is a histone deacetylase inhibitor, the first of a new class of antineoplastics. Romidepsin will be marketed as Istodax® by Gloucester Pharmaceuticals. ■