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INSIDE

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Cholinergic Autonomic Dysfunction in Veterans with Gulf War Illness

ABSTRACT & COMMENTARY

By Norman Latov, MD, PhD

Professor of Neurology, Department of Neurology, and Professor of Neuroscience, Brain and Mind Research Institute, Weill Cornell Medical College

Dr. Latov has served as a consultant to Griffols, Novartis, CSL Behring, Baxter Therapeutics, Pfizer, and Merck, and has stock in Therapath LLC.

Synopsis: *Veterans with Gulf War illness had a statistically significant increase of autonomic symptoms, heart rate variability, and abnormalities in sudomotor function, as measured by the Quantitative Sudomotor Axon Reflex Test, compared to control subjects. The study found objective autonomic deficits in veterans with the Gulf War syndrome with autonomic syndrome.*

Sources: Haley RW, et al. Cholinergic autonomic dysfunction is veterans with Gulf War illness. *JAMA Neurol* 2013;70:191-200.

Freeman R. Objective evidence of autonomic dysfunction and the role of stress in the Gulf War syndrome. Editorial. *JAMA Neurol* 2013;70:158-159.

In a nested case-control study, the authors evaluated autonomic symptoms and functions in a representative sample of veterans meeting validated case definition of Gulf War illness, and compared these to autonomic symptoms and functions in a control population consisting of a representative sample of randomly selected subjects from a U.S. military health survey. Validated outcome measures included the Autonomic Symptoms Profile Questionnaire, Composite Autonomic Severity Score, heart rate variability in a 24-hour electrocardiogram, and Quantitative Sudomotor Axon Reflex Test (QSART). The study found that veterans with the Gulf War illness had a significant increase of autonomic symptoms compared to controls including in orthostatic intolerance, secretomotor symptoms, upper gastrointestinal and urinary dysfunction, autonomic diarrhea or constipation, sleep disturbances, pupilomotor and vasomotor abnormalities, and erectile dysfunction. These were most consistent with cholinergic autonomic dysfunction. The autonomic symptoms correlated

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with objective measures of impairment in the Quantitative Sudomotor Axon Reflext Test (QSART) and high frequency of heart rate variability in a 24-hour electrocardiogram. The accompanying editorial discusses the potential role of stress in the development of autonomic dysfunction.

■ COMMENTARY

The authors note that subjects with the Gulf War syndrome exhibited a reduction in sudomotor function that was most severe in the feet, indicating a length-dependent peripheral nerve deficit. Of note is that veterans with Gulf War illness also have a significantly higher incidence of fibromyalgia, the symptoms of which can overlap with those of small fiber neuropathy, in which there is degeneration of both autonomic and sensory nerve fibers.[1] The cause is unknown, but prolonged exposures to organophosphates or hydrocarbon fumes have been implicated.[2] Both are neurotoxic agents that can cause axonal degeneration.[3,4] Additional studies, such as quantification of sudomotor innervation of sweat glands in skin biopsy specimens,[5] might provide further insight regarding the neuropathological basis of the autonomic dysfunction.

This study is the first to provide objective evidence of organic disease in veterans with the Gulf War Illness, a syndrome that has been regarded by many to be largely psychosomatic. Further investigations into the pathological and physiological changes that are associated with this illness would help elucidate the responsible mechanism and develop more effective treatments and preventive measures. ■

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Editorial E-Mail: leslie.coplin@ahcmedia.com
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Questions & Comments
Please call **Leslie Coplin**, Executive Editor, at leslie.coplin@ahcmedia.com.

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Mild Head Strike May Have Lasting Impact on Children and Adolescents

ABSTRACT & COMMENTARY

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a retained consultant for Boehringer Ingelheim and Bayer, and is on the speakers bureau for Boehringer Ingelheim.

Synopsis: *Almost a third of children and adolescents seen in the emergency department with mild traumatic brain injury develop postconcussion syndrome, with migraine-like headaches as the most common symptom.*

Sources: Babcock L, et al. Predicting postconcussion syndrome after mild traumatic brain injury in children and adolescents who present to the emergency department *JAMA Pediatr* 2013;167:156-161.

Butler IJ. Postconcussion syndrome after mild traumatic brain injury in children and adolescents requires further detailed study. *JAMA Neurol* 2013; March 25:1-2. doi:10.1001/jamaneurol.2013.2801 [Epub ahead of print].

Kuczynski A, et al. Characteristics of post-traumatic headaches in children following mild traumatic brain injury and their response to treatment: A prospective cohort. *Dev Med Child Neurol* 2013; Apr 5. http://dx.doi.org/10.1111/dmcn.12145.

MILD TRAUMATIC BRAIN INJURY (MTBI) IN CHILDHOOD AND adolescence often occurs as a sports injury or after a fall, and can result in disabling symptoms of postconcussion syndrome (PCS), including post-traumatic headaches (PTH). A definition of mTBI developed by the Mild Traumatic Brain Injury Committee of the American Congress of Rehabilitation Medicine is a blow to the head or accel-

eration/deceleration movement of the head resulting in one or more of the following: loss of consciousness for < 30 minutes, amnesia of < 24 hours or any alteration in mental state, and a Glasgow Coma Scale score of ≥ 13 measured 30 minutes or more after injury.

Babcock et al did a retrospective analysis of a prospective observational study to determine the acute predictors associated with the development of PCS in children and adolescents after mTBI. Four hundred six children and adolescents, ages 5 to 18 years, presented to the pediatric emergency department (ED) at the University of Rochester Medical Center. The Rivermead Post Concussion Symptoms Questionnaire (RPQ) was administered to compare the severity of symptoms present at 3 months after the injury to symptoms that had occurred prior to the injury. Common PCS symptoms included headaches, dizziness, nausea, noise sensitivity, sleep disturbance, fatigue, irritability, depression, frustration, poor memory, poor concentration, taking longer to think, blurred vision, light sensitivity, double vision, and restlessness. PCS was defined as the presence of three or more of these symptoms on the RPQ that were rated as worse than before the injury. Of the patients presenting to the ED with mTBI, 29.3% developed PCS. Headache was the most common symptom after the injury noted on the RPQ, reported by 30.5%. Significant acute predictors for PCS, while controlling for other factors, were adolescent age (odds ratio [OR], 2.00; 95% confidence interval [CI], 1.07-3.73), presence of headache (OR, 2.63; CI, 1.52-4.57), and admission to the hospital (OR, 2.90; CI, 1.48-5.68). All patients experienced considerable school absenteeism after the TBI, but those who developed PCS missed a mean (SD) of 7.4 (13.9) days.

In the experience of Ian Butler, MD, a pediatric neurologist who commented on the Babcock study, the clinical manifestations of PCS usually resolve in 3-6 months; however, behavioral and cognitive changes may take longer (1-2 years). He noted that children with an underlying calcium channelopathy may have delayed severe neurological sequelae after mTBI, out of proportion to the degree of trauma. Given the association between calcium channel disorders and neurological sequelae after mTBI, Butler predicted that gene testing for calcium or other channelopathies eventually may help in predicting outcome after mTBI in children.

Kuczynski et al described the clinical characteristics and response to treatment of PTHs in a prospective cohort of children with mTBI presenting to an ED in Canada. A prospective longitudinal ED cohort with mTBI (n = 670; 385 males, 285 females) was compared to a group of children with extracranial injury (n = 120; 61 males, 59 females). A retrospective chart review of a separate cohort of children from a brain injury clinic (the treatment cohort) treated for PTH was also performed (n = 44; 29 females, 15 males; mean age 14 years 1 month, SD 3 years 1 month). The median time since mTBI was 6.9 months (range 1-29 months) in the treatment group. The mean follow-up interval after treatment started was 5.5 weeks (SD 4.3 weeks). Among the ED cohort (n = 39; 20 males, 19 females; mean age 11 years 1 month, SD 4 years 3 months), 11% of children were symptomatic with PTHs at a mean of 15.8 days (SD 11.6 days) after injury. The morbidity associated with PTH was significant, with 44% and 61% of children in the ED and clinic cohorts, respectively, experiencing daily headaches. Three months after mTBI, 7.8% of children complained of headaches of multiple types (including tension-type, cervicogenic, and occipital neuralgias), with 55% of the mTBI headaches meeting the criteria for migraine. A majority (56%) of children with PTH had pre-existing headaches, with 18% having pre-trauma migraines. A family or past medical history of migraine was present in 82% of cases. Medications used for treatment included amitriptyline, flunarizine (not available in the United States), topiramate, and melatonin, with an overall response rate of 64%.

■ **COMMENTARY**

A significant proportion of children who experience mTBI develop neurocognitive symptoms that cause disability with a major impact on school, social and sports activities, and interactions with friends and family. Identification of which children are at greatest risk of PCS should lead to early intervention and consultation with a specialist to prevent headaches and to individualize treatment of mood and behavioral symptoms. Those children who have prior migraine headaches or a family history of migraine appear to be particularly vulnerable after mTBI and should be watched for the development of PTHs so that preventive medications can be initiated early, before disability escalates. Although many of the symptoms of PCS dissipate with time, not treating the disabling symptoms early and aggressively may cause loss of scholastic and social opportunities that could impact the young person's life years after the injury. ■

Utility of Follow-Up MRI for Sciatica

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: *After successful treatment of sciatica, routine follow-up MRI of the lumbar spine provides no useful*

Secondary Prevention after Acute Ischemic Stroke

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

Closure of Patent Foramen Ovale in Selected Patients with Cryptogenic Stroke May Be Better Than Medical Therapy Alone

Source: Carroll JD, et al, for the RESPECT Investigators. Closure of patent foramen ovale versus medical therapy after cryptogenic stroke. *N Engl J Med* 2013;368:1092-1100.

Up to one-third of all ischemic strokes do not have a defined etiology and are referred to as cryptogenic, and about one-half of those have a patent foramen ovale (PFO). It is uncertain if closure of a PFO is effective in preventing recurrent stroke or is better than medical therapy. The CLOSURE I trial evaluated the STARFlex Septal Closure System and failed to show superiority of closure over medical therapy alone.[1] The investigators in the Randomized Evaluation of Recurrent Stroke Comparing PFO Closure to Established Current Standard of Care Treatment (RESPECT) trial evaluated the effectiveness of the Amplatzer PFO Occluder to prevent recurrent stroke and compared this intervention to standard medical therapy with antiplatelet and antithrombotic medications.

A total of 980 patients (mean age = 45.9 years) were enrolled and randomized in a 1:1 ratio to medical therapy alone or closure of the PFO. The medical therapy group received one or more antiplatelet medications (74.8%) or warfarin (25.2%). The closure group was followed over 1375 patient-years and the medical group over 1184 patient-years, with a higher dropout rate in the medical group. In the intention-to-treat analysis, recurrent stroke occurred in nine patients in the closure group and 16 patients in the medical group (hazard ratio with closure, 0.49; 95% confidence interval [CI], 0.22-1.11; $P = 0.08$). In the prespecified, per-protocol cohort (six events in the closure group vs 14 events in the medical group), the hazard ratio was 0.37 (95% CI, 0.14-0.96; $P = 0.03$). Serious adverse events occurred in 23% of patients in the closure group and in 21.6% in the medical therapy group. Procedure-related adverse events occurred in 21 of 499 patients in the closure group (4.2%), but the rate of atrial fibrillation or device thrombus was not increased.

In the primary intention-to-treat analysis, there was no significant benefit associated with closure of the PFO

information. Recurrent or persistent symptoms mandate additional evaluation based on clinical symptoms and signs.

Source: el Barzouhi A, et al. Magnetic resonance imaging in follow-up assessment of sciatica. *N Engl J Med* 2013;368:999-1007.

Afflicting 80% of americans at some point in their lives, and 50% in any given year, low back pain is the second leading cause for physician visits in this country, the third leading cause for surgical procedures, the fifth leading cause for hospitalizations, and accounts for more than $24 billion a year in direct medical costs. Best practices that might positively impact these statistics would be welcome, and the present study, examining the value of obtaining follow-up magnetic resonance imaging (MRI) at 1 year in patients with persistent sciatica and known to have lumbar-disc herniation, is a first step in this direction.

Patients in this study had participated in a multicenter, randomized trial comparing conservative management to surgery for lumbar disc herniation with sciatica, having been eligible if they experienced 6-12 weeks of sciatica and demonstrated disc herniation on MRI, with pain in a dermatomal distribution associated with neurologic findings corresponding to the nerve root affected on imaging. MRI was performed at baseline and repeated at 1 year. Complete or near complete resolution of patient-reported symptoms at 1 year, using the 7-point Likert self-rating scale of global perceived recovery, was defined as a favorable outcome, and was measured at baseline and at 2, 4, 8, 12, 26, 38, and 52 weeks. Patients were blinded to the results of their MRI findings and prior assessments. Statistical analysis included student's t-test and logistic regression models, and model-based multiple imputation was used to account for missing data.

Among 599 patients screened for the trial, 283 were randomized, and after 1 year, 267 were available for a second MRI (94.3%). Of these 267 patients, 131 had been randomized to surgery, of which 15 recovered before surgery,

in adults who had a cryptogenic ischemic stroke, but closure was superior to medical therapy, alone, in a prespecified, per-protocol cohort in the "as-treated" analysis. ■

Reference

1. Furlan AJ, et al. Closure or medical therapy for cryptogenic stroke with patent foramen ovale. *N Engl J Med* 2012;366:991-999.

Use of Ischemic Stroke Scores May Aid in the Prediction of Risk of Early Recurrence

Source: Maier IL, et al. Risk prediction of very early recurrence, death and progression after acute ischemic stroke. *Eur J Neurol* 2013;20:599-604.

The investigators studied the utility of three common stroke risk scores to determine the risk of early recurrence after acute ischemic stroke: Essen Stroke Risk Score (ESRS),[1] the ABCD^2 score,[2] and the Recurrence Risk Estimator at 90 days (RRE-90).[3] Clinical and radiographic data were analyzed from 1727 consecutive patients admitted to the stroke unit at the University of Gottingen, Germany, and evaluated retrospectively. The predictive value of three stroke scores was tested for early recurrence within 7 days, as well as death and progressive stroke.

Early recurrent stroke occurred in 56 patients (3.2%), 40 patients (2.3%) died, and 125 patients (7.2%) had progressive stroke within the first 7 days. The ESRS was not predictive for early recurrence, death, or progressive stroke. The ABCD^2 score was predictive for death ($P < 0.001$) and progressive stroke ($P < 0.001$), and the RRE-90 was predictive for early recurrent stroke ($P < 0.001$), early death ($P < 0.001$), and progressive stroke ($P < 0.001$).

The ABCD^2 score and the RRE-90 show promise in predicting early recurrence, as well as death and progression in the first 7 days following acute ischemic stroke. Further validation of these findings in other stroke cohorts should be performed. ■

References

1. Fitzek S, et al. The Essen Stroke Risk Score in one-year follow-up acute ischemic stroke patients. *Cerebrovasc Dis* 2011;31:400-407.
2. Chandratheva A, et al. ABCD2 score predicts severity rather than risk of early recurrent events after transient ischemic attack. *Stroke* 2010;41:851-856.
3. Ay H, et al. A score to predict early risk of recurrence after ischemic stroke. *Neurology* 2010;74:128-135.

and 136 were randomized to receive conservative care, of which 54 underwent surgery within the first year. At 1 year, a favorable outcome was achieved in 84%, based on the 7-point Likert scale. In the as-treated analysis, a herniated disc was present at 1 year in 21% of patients treated surgically and 60% of those treated conservatively. In the intention-to-treat analysis, a herniated disc was present in 22% of the former and 47% of the latter. Among those with a favorable outcome, 35% demonstrated disc herniation on MRI at 1 year, compared to 33% among those with an unfavorable outcome, with nerve root compression visible on imaging in 24% and 26%, respectively. Of 170 patients who had surgery, 88% (150) demonstrated a visible scar on MRI, of which 86% reported a favorable outcome, compared to 75% with no scar ($P = 0.19$). Among those with a definite, probable, or possible disc herniation, favorable outcome was reported in 85% at 1 year, compared to 83% among those with no disc herniation. Follow-up MRI at 1 year did not distinguish between those who improved and those who did not, and MRI is not warranted in this clinical setting as a routine follow-up examination.

■ COMMENTARY

How does the utility of electrodiagnostic studies (EMG) compare with MRI in patients with radicular leg pain? Among 152 subjects with sciatica for at least 6 weeks' duration and no prior history of surgery, malignancy, autoimmune disease, or trauma, MRI and EMG were abnormal in 104 (68.4%), whereas both were normal in 10 (6.5%). MRI alone was abnormal in 30 patients (19.7%) while EMG was the sole abnormal test in 21 (13.8%). EMG can be of value in MRI-negative sciatica patients.[1] ■

Reference

1. Hasankhani EG, Omidi-Kashani F. Magnetic resonance imaging versus electrophysiologic tests in clinical diagnosis of lower extremity radicular pain. *ISRN Neuroscience* 2013; Available at: http://dx.doi.org/10.1155/2013/952570). Accessed April 16, 2013.

Exercise Benefits Patients with Parkinson's Disease

ABSTRACT & COMMENTARY

By Jeffrey Gross, MD

Clinical Associate Professor of Rehabilitation Medicine, NYU School of Medicine, Adjunct Clinical Assistant Professor of Rehabilitation Medicine, Weill Cornell Medical College

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

Synopsis: *Exercise, both aerobic as well as stretching and strengthening, improves motor function and gait in patients with Parkinson's disease.*

Source: Shulman LM, et al. Randomized clinical trial of 3 types of physical exercise for patients with Parkinson disease. *JAMA Neurol* 2013;70:183-190.

There is growing interest in the use of exercise training to improve mobility and function in patients with early Parkinson's disease (PD). A recent literature review showed that there were 75 clinical trials of physical training for PD.[1] The results of these trials have been promising. However, the majority of the studies were limited by methodological flaws.

Shulman et al performed a prospective, randomized, single-blind, parallel-group clinical trial of efficacy of three types of physical exercise for PD: 1) higher-intensity treadmill (HITM), 2) lower-intensity treadmill (LITM), and 3) stretching and resistance (SR). The primary objective of this clinical trial was to compare the efficacy of these three types of physical exercise to improve gait, fitness, and strength in patients with PD. The additional objectives were to study the efficacy of exercise to reduce disability and nonmotor symptoms in PD. The criteria for eligibility included a diagnosis of PD with no atypical signs or exposure to dopamine-blocking drugs, a Hoehn and Yahr stage of 1 to 3, the presence of mild-to-moderate gait or balance impairment, an age of 40 years or older, and no significant dementia. Exclusion criteria were unstable medical or psychiatric comorbidities, orthopedic conditions restricting exercise, or active participation in a regular exercise program before enrollment.

A screening treadmill exercise test was used to determine cardiopulmonary safety and neuromotor capacity to participate. The total duration of the study was 4 months. Initial evaluations included medical history and physical and neurologic examinations. Baseline and post-training assessments were performed by physicians and staff blinded to participants' treatment group. All evaluations were undertaken while the participants were in the "on" periods from medications,or within 3 hours of medication dosing.

Pre- and post-training maximum oxygen ventilation (VO_2 max) was assessed during treadmill exercise with the endpoint being voluntary exhaustion. Gait assessments were performed before and after training. The 6-minute walk (6MW) was the primary motor outcome measure. Participants were instructed to cover as much distance as possible in 6 minutes, turning every 30 meters. Other gait measures were two 10-meter walks (self-selected and fastest comfortable pace) and a 15-meter fast gait. Muscle strength was assessed with a 1-repetition maximum strength test performed before and after training in all study groups for leg press and leg extension. Strength in each leg was tested separately on isotonic weight machines. Disability and physical activity assessments were tabulated. Nonmotor symptom assessments also were performed before and after training.

Sixty-seven participants in the study were randomized into three groups that trained three times per week for 3 months under the direct supervision of exercise physiologists. Vital signs were monitored. All participants wore a non-weightbearing harness to eliminate the risk of falls. The HITM group exercised up to 30 minutes at a speed and incline that eventually resulted in a heart rate of 70-80% of their maximum (220-age). The LITM group walked at a comfortable pace for up to 50 minutes. The incline and speed remained constant. Their heart rate remained in the range of 40-50% of their calculated maximum. The SR group did two sets of 10 reps on leg extension, leg press, and leg curl machines. Weight was increased as tolerated. Stretching was performed as well.

There were no serious adverse events during the study. The results revealed improvements in all three groups for the 6MW. The greatest gains were made by the LITM group (12%), followed by the SR (9%) and the HITM (6%) groups, but the differences were not statistically significant between groups. The LITM group also made significant gains in the other gait measurements. VO_2 max increased in only the HITM and LITM groups. Lower extremity muscle strength only increased in the SR group. No significant changes were noted in disease severity, disability, or nonmotor symptoms in any of the groups.

■ COMMENTARY

The above results confirm the value of a regular exercise program for PD patients in the early stage of disease. Low-intensity treadmill exercise was proven to be safe, well tolerated, and beneficial in improving function and cardiovascular fitness. Resistance exercise leads to increased strength, as would be expected. A combination of these interventions seems warranted in all early PD patients who are medically well and able to participate. Although the

exercise programs did not result in improvements in disability or quality of life, these variables did not deteriorate during the study either. This reflects the study's main limitation — there was no non-exercise control group. ■

References

1. Mehrholz J, et al. Treadmill training for patients with Parkinson's disease. *Cochrane Database Syst Rev* 2010;(1):CD007830.

One Step to Understanding Psychogenic Dystonia

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, PhD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical College

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

Synopsis: *Regional cerebral blood flow defines distinct patterns of disrupted metabolism in psychogenic vs "organic" dystonia, with decreased flow in motor and premotor cortex in psychogenic dystonia, but increased flow in subcortical structures.*

Source: Schrag AE, et al. The functional neuroimaging correlates of psychogenic versus organic dystonia. *Brain* 2013;136(PT 3):770-781.

This study compares functional imaging of adult study participants with psychogenic dystonia, genetic dystonia, and healthy controls. Participants with psychogenic dystonia comprised six individuals who fulfilled accepted diagnostic criteria, were recruited by experienced movement disorders neurologists, had no serious medical comorbidity or major affective or psychotic disorders, and were without structural abnormalities on brain and cervical-spine MRI. As subjects with "organic" dystonia, five individuals with genetic dystonia associated with DYT1 gene mutation were enrolled, of whom four had generalized symptoms and one had mild foot and hand dystonia. Six matched healthy control subjects were included. All participants underwent $H_2{}^{15}O$ PET to assess regional cerebral blood flow (rCBF), averaged over three conditions: 1) at rest, 2) with the right foot inverted and plantar flexed (voluntarily for DYT1 and control subjects), and 3) with monitored paced ankle flexion-extension. When compared to controls, in psychogenic dystonia rCBF was increased in bilateral cerebellum, left globus pallidus pars interna, right caudate, and bilateral thalamus, and was decreased in left primary motor cortex (medial leg area), left supplementary motor area, and left thalamus. When compared to subjects with DYT1-associated dystonia, in psychogenic dystonia rCBF was increased in the cerebellum, putamen, thalamus, and the left subthalamic nucleus. In contrast, in DYT1-associated dystonia compared with psychogenic dystonia, rCBF was increased in the left primary motor cortex (medial leg area) and left premotor cortex, right parietal cortex, as well as right thalamus, and right caudate nucleus.

■ COMMENTARY

Psychogenic movement disorders are challenging to diagnose and treat, and are common. It has been estimated that up to 30% of outpatient neurology referrals comprise cases in which neurological symptoms cannot be accounted for medically. Unfortunately, there are no objective tests that confirm a diagnosis of psychogenic disorder. Moreover, in suspected psychogenic dystonia, diagnosis is hampered by limitations of tests that confirm a known cause of dystonia, such as genetic mutation or cerebral structural abnormalities. Various criteria have been proposed, including those used in this study, by Gupta and Lang in 2009.[1] According to the diagnostic classification, features supporting the diagnosis would involve symptom improvement with suggestion, placebo, psychotherapy, physiotherapy, or while "unobserved," and a "clinically established" diagnosis would involve features that do not fit with a known clinical condition, with "false" signs, psychiatric disturbance, and multiple somatizations. Other clues from physical examination include variability of symptoms, distractibility, and suggestibility. Although such formal criteria are highly valuable, they also highlight the limited understanding of psychogenic disease and the critical need to better understand, diagnose, and track treatment effects in these disorders. Again, dystonic symptoms present a particular challenge as dystonia may fluctuate and appear bizarre at times, and psychiatric disease is common enough that it is not a reliable enough indicator of a psychogenic etiology. As such, the present study is very important in that it is the first to focus specifically on psychogenic dystonia. Moreover, the study included a very homogeneous cohort in terms of physical presentation — with fixed dystonia of a lower limb chosen as characteristic of psychogenic dystonia based on prior studies. The investigators found that rCBF measures clearly highlight anatomically distinct differences between both psychogenic and "organic" dystonia, and also between psychogenic dystonia and control participants.

The finding that rCBF is decreased in primary motor cortex but increased in basal ganglia and cerebellum in psychogenic vs "organic" dystonia leads the authors to

propose a cortical-subcortical differentiation. It is therefore very interesting that organic dystonia, but not psychogenic dystonia, has been associated in previous studies with increased cortical plasticity. Although the study has obvious weaknesses, including small numbers of participants and diagnoses in psychogenic cases made on a clinical basis, it does provide hope for developing better understanding of underlying mechanisms and testing methodologies. ■

Reference

1. Gupta A, Lang AE. Psychogenic movement disorders. *Curr Opin Neurol* 2009;22:430-436.

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:

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5. Once the completed evaluation is received, a credit letter will be e-mailed to you instantly. You will no longer have to wait to receive your credit letter!

CME Questions

1. Gulf War syndrome has been postulated to be caused by all of the following *except*:
a. organophosphate exposure delayed neuropathy.
b. hydrocarbon fumes inhalation.
c. post-traumatic stress disorder.
d. traumatic injuries.
e. fibromyalgia syndrome.

2. Which statement best describes headaches after mTBI in children?
a. Headaches rarely occur after mTBI.
b. The most common headache type after mTBI is tension-type headache.
c. Headaches after mTBI are frequently associated with a family or personal history of migraine.
d. Headaches after mTBI occur only a few times a month.
e. Headaches after mTBI disappear by 3 months.

3. Among patients who undergo surgery for lumbar disc herniation and are pain free, or almost so, which of the following is true 1 year after presentation?
a. Lumbar magnetic resonance imaging (MRI) shows that they are more likely to *not* have a visible scar than to have a scar on MRI.
b. Lumbar MRI shows that they are more likely to have a visible scar than *not* to have a visible scar on MRI.
c. Lumbar MRI shows that the presence of scar on MRI does *not* predict outcome.
d. Due to bone artifact, MRI scan is not sensitive enough to demonstrate scar formation at a surgical site

4. Which of the following is false regarding Parkinson's disease?
a. High-intensity treadmill exercise improves gait speed.
b. Low-intensity treadmill exercise improves gait speed.
c. Stretching and strengthening improve gait speed.
d. Exercise reduces disability in Parkinson's disease.

5. When compared with DYT1-associated dystonia, which of the following features is *not* associated with psychogenic dystonia?
a. Increased rCBF in premotor cortex correlated with increased plasticity
b. Signs and symptoms not consistent with known condition
c. Unexplained fluctuations in symptoms
d. Increased rCBF in basal ganglia and cerebellum
e. Fixed abnormal postures

6. In patients with cryptogenic ischemic stroke and PFO, closure of the PFO has been proven to be more effective in preventing recurrent stroke than medical therapy alone.
a. True
b. False

7. The Essen Stroke Risk score has not been shown to predict early recurrent stroke risk.
a. True
b. False

In Future Issues: **Update on Chronic Traumatic Encephalopathy**

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.*

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Extended Treatment of VTE with Dabigatran vs Warfarin

Source: Schulman S, et al. *N Engl J Med* 2013;368:709-718.

Current recommendations for treatment of uncomplicated venous thromboembolism (VTE) in the absence of persistent risk factors for recurrence (e.g., protein C, protein S deficiency) suggest at least 3 months of antithrombotic therapy, typically with warfarin. Risk of recurrence, however, is not insubstantial, and recent clinical trials have shown that extending the duration of antithrombotic therapy after a course of warfarin (with aspirin, for instance) reduces the risk for recurrent VTE.

When warfarin is used for extended VTE recurrence prophylaxis, serious bleeding risk is about 1% annually. In comparison trials to warfarin, major bleeding rates on dabigatran have been generally comparable to warfarin, and intracerebral bleeding was demonstrably less with dabigatran than warfarin. Since dabigatran does not require monitoring, monthly physician visits, or dietary modulation, and has infrequent potential for drug interaction, it provides an attractive alternative.

Schulman et al report the results of two randomized, controlled, double-blind trials of dabigatran 150 mg twice daily vs warfarin or placebo in patients who had completed at least 3 months of warfarin treatment. Dabigatran was found to be noninferior to warfarin for prevention of recurrent VTE, with less frequent bleeding than warfarin (0.9% vs 1.8%). Dabigatran may be a viable alternative for extending DVT prophylaxis after a "traditional" course of warfarin. ■

Selection Criteria for Lung Cancer Screening

Source: Tammemagi M, et al. *N Engl J Med* 2013;368:728-736.

The national lung screening trial (NLST) reported in 2011 that low-dose CT screening in selected smokers (n = 53,454) reduced mortality from lung cancer by 20%. Entry criteria for the NLST included age 55-74 years with at least a 30 pack-years smoking history (former smokers, if they had quit within the last 15 years, were also enrolled). Subsequently, national organizations have variously endorsed lung cancer screening for persons matching NLST eligibility criteria.

The Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) developed a lung-cancer risk prediction model based on 154,901 subjects. The PLCO determined other predictors of lung cancer beyond age and smoking duration used in the NLST, including body mass index, family history of lung cancer, and presence of chronic obstructive pulmonary disease. Because the PLCO duration of follow-up was longer than NLST (9.2 years vs 6.5 years), the strength of the PLCO prediction model might be anticipated to be greater than NLST.

A comparison between the NLST and PLCO prediction models found that the PLCO criteria had greater sensitivity and specificity, ultimately missing 43% fewer lung cancers than NLST. The PLCO prediction model has the potential to improve outcomes for persons at risk of lung cancer. ■

Special Subgroups in Hypertension: Obese Hypertensives

Source: Weber MA, et al. *Lancet* 2013; 381:537-545.

The inter-relatedness of obesity, hypertension, and cardiovascular (CV) events is complex. Obesity is independently associated with high blood pressure, all-cause mortality, and CV mortality. Yet, some reports have suggested that when parsing out CV events among a secondary prevention population (persons with *existing* CV disease), subjects with *normal* body weight bear a disproportionately *greater* risk than overweight and obese persons.

To further clarify this counterintuitive knowledge base, Weber et al report on an analysis of the Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension trial (ACCOMPLISH). ACCOMPLISH was performed to determine the relative efficacy of an angiotensin-converting enzyme (ACE) inhibitor + hydrochlorothiazide (HCTZ) vs ACE + amlodipine (CCB) in patients (n = 11,506) with Stage 2 hypertension (blood pressure > 160 mmHg). The trial ultimately demonstrated that ACE + CCB provided a significant mortality advantage over ACE + HCTZ.

In this report, ACCOMPLISH study subjects were divided into normal weight (body mass index [BMI] < 25), overweight (BMI 25-29), and obese categories (≥ BMI 30). CV events were most

frequent in the normal weight group, and least frequent in the obese patients in the ACE + HCTZ arm of the trial. In the ACE + CCB arm, there were no differences between weight categories in outcomes.

The seemingly paradoxical relationship between overweight and outcomes in persons with established CV disease (myocardial infarction, cerebrovascular accident, or existing hypertension) is difficult to explain. It may be that obesity-related hypertension is mediated by a different, more benign pathophysiology, hence producing more favorable outcomes, although this concept has been insufficiently explored. Finally, because of relatively higher event rates with ACE + HCTZ in normal-weight patients, clinicians should select ACE + CCB since event reduction is equivalent across weight groups for this combination. ■

Omalizumab for Asthma in Real Life

Source: Grimaldi-Bensouda L, et al. *Chest* 2013;143:398-405.

In evidence-based medicine terminology, "efficacy" is the term used to reflect results achieved within a clinical trial, whereas "effectiveness" indicates the results seen in "typical practice settings," commonly called "real-life settings." Clinical trials are anticipated to provide results superior to those in practice settings, where patients cannot be so readily de-selected or excluded, where resources may be more limited, and where rigorous regimentation for administration of treatment is less abundant.

Omalizumab (OMA) is not generally regarded as a first-line asthma medication, but rather an appropriate add-on when guideline-based foundation therapies (inhaled steroids, long-acting beta agonists, and leukotriene receptor antagonists) are insufficient to provide control. Although only 30-50% of asthmatics have a prominent underlying allergic component, among difficult-to-control asthmatics, the number may be as high as 80%. Clinical trials indicate that OMA, by blocking IgE, is a useful add-on in such resistant asthma cases. But do "real-life" settings reflect similar benefit?

Grimaldi-Bensouda et al report on refractory asthma patients (n = 767) recruited by more than 100 physicians who prescribed OMA as an add-on treatment. During a follow-up period of almost 2 years, study subjects who received any doses of OMA enjoyed a 43% relative risk reduction in likelihood of hospitalization or emergency department visits for asthma. Subjects on treatment with OMA demonstrated an even greater benefit: 60% relative risk reduction.

In real-life settings, OMA provides substantial improvement in clinically important endpoints for patients with difficult-to-treat asthma. ■

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

Subscriber Information
Customer Service: 1-800-688-2421
E-Mail Address: neill.kimball@ahcmedia.com
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Address Correspondence to: AHC Media, 3525 Piedmont Road, Building Six, Suite 400, Atlanta, GA 30305.

Tenofovir: New Hope for Hepatitis B Patients

Source: Marcellin P, et al. *Lancet* 2013; 381:468-475.

Hepatitis B (HEP-B) is responsible for approximately half of hepatic carcinoma cases worldwide. While HEP-B treatment has been shown to reduce risk for liver failure and hepatic cancer in cirrhosis, whether currently available antiviral therapies actually reverse the underlying disease process is less well studied. Indeed, previous prevailing wisdom had opined that the fibrotic changes of cirrhosis might not be amenable to attempts at regression.

Tenofovir (TFV) is a potent HEP-B polymerase/reverse transcriptase inhibitor. Marcellin et al report on the results of an open-label trial of TFV in patients who had completed a 48-week antiviral treatment with either adefovir or TFV. Subjects were subsequently assigned to once-daily TFV for up to 7 years. Approximately one-fourth of patients had cirrhosis at baseline, and all subjects agreed to follow-up liver biopsy in the fifth year of the trial (240 weeks).

TFV was well tolerated and confirmed to be associated with regression of fibrosis (in the cirrhosis group) and improvement in liver histology (in the non-cirrhosis group) at 240 weeks. This large dataset is very supportive of a role for TFV not just in arresting disease progression, but actually in regression of cirrhosis. ■

H. pylori: Frequency of Recurrence After Successful Eradication

Source: Morgan DR. *JAMA* 2013;309: 578-586.

Worldwide, *Helicobacter pylori* appears to be responsible for the majority of cases of gastric cancer. A Chinese clinical trial of *H. pylori* eradication through pharmacotherapy noted an almost 40% reduction in gastric cancer over the subsequent 15-year observation period. Initial eradication of *H. pylori* provides important risk reduction. Of course, initial treatment is sometimes not effective, and even when initial treatment is effective, there is potential for recurrence.

From a population of study subjects (n = 1091) cleared of *H. pylori* (confirmed by post-treatment negative urea breath tests), only 125 evidenced recurrence over a 1-year follow-up (11.5%). Factors associated with recurrence included non-adherence to *H. pylori* treatment regimens and methodology of the treatment regimen (i.e., 14-day triple therapy, sequential therapy, or concomitant therapy, with sequential therapy being most successful). These recurrence rates are typical of low-income countries, whereas recurrence rates are as much as 30% less in high-income countries. Overall, *H. pylori* treatment is well tolerated, provides important risk reduction for gastric cancer, and is associated with few recurrences that can be managed by appropriate retreatment. ■

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.*

New Study on Chelation Therapy Proves Controversial

In this issue: Chelation therapy for cardiovascular disease; statins and kidney injuries; chlorthalidone for hypertension; and FDA actions.

Does chelation therapy work?

The National Center for Complementary and Alternative Medicine (NCCAM) is attempting to fulfill its mandate to prove or disprove the value of alternative treatments. A division of the National Institutes of Health, NCCAM has done research on everything from supplements to meditation. This latest study looks at chelation therapy in patients with cardiovascular disease. Chelation therapy with ethylene diamine tetra-acetic acid (EDTA) has been used for decades to treat lead toxicity, and it has also been found to reduce metastatic calcium deposits. Despite the fact that small studies have never shown a benefit for chelation in treating cardiovascular disease, many alternative clinics continue to tout its value in this role. A recently published NCCAM-funded study to evaluate the value of chelation enrolled more than 1700 patients ≥ 50 years of age with a history of myocardial infarction (MI) at least 6 weeks prior. The study was a double-blind, placebo-controlled, 2 × 2 factorial randomized trial from 2003 through 2011. There were 289 patients who withdrew consent from the study, of which 60% were in the placebo group. The study consisted of 40 EDTA/vitamin infusions vs placebo infusions (given weekly for 30 weeks then at 2-8 week intervals). About 15% of patients in both groups dropped out during therapy. The primary outcome was a composite of total mortality, recurrent MI, stroke, coronary revascularization, or hospitalization for angina. The primary endpoint occurred in 222 (26%) in the chelation group and 261 (30%) in the placebo group (hazard ratio [HR], 0.82; 95% confidence interval [CI], 0.69-0.99; $P = 0.35$). There was no effect on total mortality, but there was slight improvement in other outcomes with chelation. The authors conclude that among stable patients with a history of MI, chelation therapy modestly reduced the risk of adverse cardiovascular outcomes. They conclude that this study provides evidence to guide further research but is not sufficient to support the routine use of chelation therapy in patients with cardiovascular disease (*JAMA* 2013;309:1241-1250). Editorialists in the same issue of *JAMA* immediately leveled strong criticisms, ranging from allegations of noncompliance with regulations for the protection of research participants to questioning the professional credentials of the study sites and investigators. The *JAMA* editorial board did an extensive review of the data, and despite concerns, decided to publish the study with the caveat that "these findings do not support the routine use of chelation therapy as secondary prevention for patients with previous myocardial infarction and established coronary disease." (*JAMA* 2013;309:1291-1292.) Another editorialist, however, suggests that "limitations in the design and execution" of this trial compromise the findings. For example, the high number of withdrawals of consent in the placebo group suggests that the study was not truly blinded. There is also concern about the use of "softer" endpoints such as coronary revascularization and hospitalization for angina.

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

Also, the trial design was altered midway through the study because of the length of the trial. Given these concerns, "including missing data, potential investigator or patient unmasking, use of subjective endpoints, and intentional unblinding of the sponsor, the results cannot be accepted as reliable and did not demonstrate a benefit of chelation therapy." (*JAMA* 2013;309:1293-1294.) ■

Statins and renal function

When prescribing a high-dose statin, physicians no longer need to monitor liver function tests, but might want to consider monitoring renal function, at least for the first 3 months. Last year, the FDA removed labeling requiring periodic monitoring of liver enzyme tests, but now a Canadian study suggests that high-potency statins (defined as doses of at least 40 mg simvastatin, 20 mg atorvastatin, or 10 mg rosuvastain) may be associated with acute kidney injury. Researchers reviewed records of more than 2 million patients from nine population-based cohort studies comparing current and past use of high-potency vs low-potency statin therapy. Patients hospitalized for acute kidney injury were matched with 10 controls. About 3% of patients had chronic kidney disease (CKD) at the onset of the study. Within 120 days of starting therapy, there were 4691 hospitalizations for acute kidney injury in patients without CKD and 1896 hospitalizations in patients with CKD. In patients without CKD, current users of high-potency statins were 34% more likely to be hospitalized with acute kidney injury compared to low-potency statin users (fixed effect rate ratio 1.34; 95% CI, 1.25-1.43). In patients with CKD, the increase was about 10% with high-potency statins (risk ratio, 1.10; 95% CI, 0.99-1.23). The authors conclude that use of high-potency statins is associated with an increased rate of acute kidney injury compared to low-potency statins, with the effect strongest in the first 120 days of treatment. The authors further suggest that since there is a relatively small incremental cardiovascular benefit between high-potency and low-potency statins, and given the increased risk of rhabdomyolysis, diabetes, and acute kidney injury, patient selection for risk-benefit is important (*BMJ* 2013;346:f880). ■

Chlorthalidone for hypertension

Thiazide diuretics are recommended as first-line treatment for hypertension. Hydrochlorothiazide (HCTZ) is the most commonly used diuretic in North America, but some experts have recommended chlorthalidone in this role, suggesting that it may be superior. A new study, however, suggests that chlorthalidone may cause more electrolyte abnormalities than HCTZ. Nearly 30,000 patients ≥ 66 years of age who were newly treated for hypertension were evaluated. About one-third were treated with chlorthalidone and the rest with HCTZ. None of the patients had been hospitalized for heart failure, stroke, or MI within the last year. The primary outcome was a composite of death or hospitalization for heart failure, stroke, or MI, and safety outcomes included hospitalization with hypokalemia or hyponatremia. After 5 years of follow-up, there was no difference in the primary outcome between the two drugs — 3.2 events per 100 person years for chlorthalidone vs 3.4 events per 100 person years for HCTZ. However, patients treated with chlorthalidone were three times more likely to be hospitalized with hypokalemia (adjusted HR, 3.06; CI, 0.81-1.06). Hyponatremia was also more common (HR, 1.68; CI, 1.24-2.28). The findings suggest that in typical doses, chlorthalidone is not associated with fewer adverse cardiovascular events or deaths compared to hydrochlorothiazide, but it is associated with a greater incidence of electrolyte abnormalities, especially hypokalemia (*Ann Intern Med* 2013;158:447-455). ■

FDA actions

The FDA has issued a warning regarding azithromycin and cardiac toxicity. The drug has been associated with fatal heart rhythms — especially in patients already at risk — including those with prolonged QT intervals, torsades de pointes, congenital long QT syndrome, bradyarrhythmias, or uncompensated heart failure. Other patients may be at risk as well, including those with low potassium or magnesium levels, those using drugs that prolong the QT intervals, and elderly patients with cardiac disease. The warning was based on a study published in *The New England Journal of Medicine* last year.

An FDA advisory committee is recommending against the use of calcitonin salmon (Miacalcin and Fortical nasal sprays, and Miacalcin injection) for the treatment of osteoporosis in postmenopausal women because the risk of cancer outweighs any potential benefit. The recommendation is based on an FDA review that questions the drug's effectiveness in reducing fractures. Another review found a small increased risk of cancer associated with the drug. The drug could still be used for Paget's disease, acute bone loss due to immobilization, and hypercalcemia. The FDA has yet to rule on the advisory committee's recommendations. ■