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INSIDE

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Neurostimulation and Cognition

ABSTRACT & COMMENTARY

Douglas Labar, MD, PhD

Professor of Neurology and Neuroscience, Weill Cornell Medical College

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

Synopsis: *Direct current transcranial stimulation of the human brain holds promise for helping to improve a variety of neurological functions, including learning and memory.*

Source: Zimerman M, et al. Neuroenhancement of the aging brain: Restoring skill acquisition in old subjects. *Ann Neurol* 2013;73:10-15.

THERE IS CONSIDERABLE INTEREST IN THE PROSPECTS FOR ENHANCING NEURAL function with stimulation devices. Zimerman et al now report transcranial direct current electrical stimulation (tDCS) improves acquisition of motor skills, particularly learning among older normal individuals.

The motor task studied was finger tapping on a four-button keyboard, acquired over 15 minutes of training, and then studied for skill retention 90 minutes and 24 hours later. The baseline rate of skill acquisition was better among 14 younger participants (mean age = 24 years) compared with 14 older participants (mean age = 68 years). When treatment with anodal tDCS over the hand knob of the motor cortex contralateral to the tested limb during training was compared with sham, the treatment produced significantly better motor skill retention at 90 minutes and 24 hours of follow-up (overall, for the combined age groups). However, when comparing 10 older with 10 younger participants, it was seen that tDCS increased the motor learning rate among the older subjects, but not in the younger subjects; tDCS had no effect in the younger individuals. It should be noted that the baseline performance in the older individuals was inferior, so they had more "room to improve" compared with the younger individuals. A performance ceiling effect also may have been operative for the younger subjects. The authors suggest that the tDCS mechanism of action was unmasking of excitatory connections within the cortex.

Over the years, numerous studies of cognitive function enhancement with varied stimulatory methods have been reported. For example, Mar-

shall et al applied tDCS bifrontally during slow-wave sleep in 30 normal subjects.[1] Recall for declarative memory items (paired associated words) presented the previous day was improved on the day after the tDCS in sleep. There was no effect if the tDCS was applied in the awake state, and no effect on procedural memory (mirror tracing) with either wake or asleep tDCS. Clark et al found in 96 subjects that 30 minutes of right inferior frontal and parietal tDCS during training accelerated identification of concealed objects in a discovery-learning paradigm.[2] Word-recognition memory was shown to be improved when vagus nerve stimulation on-phases were delivered 30 seconds after paragraph reading in patients undergoing treatment for refractory epilepsy.[3]

These above described cognitive function enhancements in normal subjects may or may not be applicable to patients with cognitive impairments from disease. Such patients (by definition) have some degree of underlying abnormal neural substrate, which may or may not be as amenable to neurostimulatory interventions as is the neural substrate in normal individuals. Nonetheless, extrapolating from experimental findings in normal subjects to plan therapies for patients may be a fruitful endeavor. An interesting example is implanted electrical stimulation of the fornix for Alzheimer's disease (AD). This began with the observation that a neurologically normal patient undergoing hypothalamic deep brain stimulation (DBS) to treat morbid obesity reported unexpected biographical memories during stimulation.[4] In this patient, memory testing for word pair recollection specifically improved significantly during stimulation-on periods, without global improvement in neuropsychological functions. Electroencephalographic (EEG) source localization revealed stimulation-induced ipsilateral hippocampal and parahippocampal activation. The authors hypothesized that these effects were mediated by stimulation of the fornix, which is a fiber bundle connecting hypothalamic, mammillary body, and septal areas to the medial temporal lobe.

Subsequently, a pilot trial of hypothalamic/fornix DBS for AD was undertaken.[5] After 6 months of DBS, four of six patients showed improvement on the AD Assessment Scale Cognitive Subscale (ADAS-Cog). After 12 months of DBS, compared with projected disease progression, two patients performed better than expected, one patient performed worse than expected, and three patients performed as expected. Medial temporal lobe activation on EEG, and reversal of impaired glucose utilization in temporal and parietal lobes on positron emission tomography, was seen in these patients, with stimulation. A multicenter clinical trial of fornix DBS for AD (four sites in the United States, one site in Canada) is underway (ClinicalTrials.gov identifier NCT01608061). There also may be therapeutic utility for noninvasive brain stimulation for AD,[6] and tDCS for post-stroke.[7]

■ COMMENTARY

These new neuromodulatory interventions seem to hold promise in a variety of cognitive function spheres. However, appropriate caution should be used before embracing these new techniques, and systematic assessment tools to detect both subtle adverse effects as well as subtle improvements are in order. Iuculano and Kadosh administered 20 minutes of tDCS (or sham stimulation) over dorsolateral prefrontal cortex (DLPFC) or posterior parietal cortex to 19 normal subjects during six daily 2-hour mathematics training sessions.[8] Posterior parietal stimulation enhanced initial mathematical skill acquisition, but impaired later quick, automatic use of mathematical skills. In contrast, DLPFC stimulation did the opposite: It impaired the initial learning process, but enhanced later automaticity for use of the learned material. Transcranial magnetic stimulation of the DLPFC is in clinical use to treat depression, and has been reported to improve[9] or disrupt[10] cognitive functions. Further research is needed to clarify the benefits and risks of these exciting new therapies. ■

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CIDP in Childhood — A Clinical Review

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical Center

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

Synopsis: *Childhood chronic inflammatory demyelinating polyradiuculoneuropathy follows a similar course as the adult counterpart and responds well to treatment with intravenous immunoglobulin.*

Source: McMillan HJ, et al. Childhood chronic inflammatory demyelinating polyradiculoneuropathy: Combined analysis of a large cohort and eleven published series. *Neuromuscul Disord* 2013;23:103-111.

How does childhood chronic inflammatory demyelinating polyradiculoneuropathy (CIDP) compare to the adult form with respect to disease onset, clinical features, long-term outcome, and response to treatment? To address this question, records of all CIDP patients seen at Boston Children's Hospital from 1989-2009 were reviewed and pooled with data from 11 previous case series spanning 1980-2009 to provide a complete review of childhood CIDP.

Inclusion criteria required a history of progressive or relapsing sensorimotor polyneuropathy in patients ≤ 19 years of age, with areflexia or hyporeflexia, fewer than 10 white cells/mm^3 in cerebrospinal fluid (CSF), and a pattern consistent with acquired demyelination in at least two nerves on nerve conduction studies (NCS), comprising slowed nerve conduction velocities, abnormal temporal dispersion or conduction block, prolonged distal latencies, and prolonged or absent F-waves. Patients were excluded if they had a family history of hereditary neuropathy, had exposure to drugs or toxins, were suspected of having a metabolic disorder, or demonstrated a sensory level or sphincteric abnormality. Clinical deficits were quantified using the modified Rankin scale, graded 0 (asymptomatic) to 6 (death). Response to treatment was defined as "good" when minimal-to-no functional impairment was reported by the treating physician, "partial" where some degree of clinical improvement was reported, and "no response" where either no clinical improvement was seen or the patient deteriorated.

At Boston Children's Hospital, 30/32 CIDP patients met all entry criteria, with two excluded due to either elevated CSF white count (13 white cells/mm^3) or equivocal NCS. Males and females were equally affected, with 60% of children demonstrating disease progression spanning more than 8 weeks, and 20% each presenting over 4-8 weeks, or < 4 weeks, mimicking Guillain-Barré syndrome. Only 30% demonstrated a monophasic course, with 70% having relapsing CIDP. Intravenous immunoglobulin (IVIG) was initially given to most, with 80% showing a good response, and long-term follow-up (mean 3.8 years) revealed that 45% were off all immunosuppressive agents with no (55%) or minimal (43%) clinical deficits. Among 143 previously published CIDP patients, the combined initial response rate for IVIG or prednisone was 79% and 84%, respectively, with only 14% responding to plasma exchange as a first-line therapy. Rankin scale improved from 3.7 to 0.7 overall. As in adults, IVIG is the treatment of choice for childhood CIDP.

■ COMMENTARY

For most patients with CIDP, maintenance therapy will be required. Cochrane Database System Reviews indicate that only class IV (insufficient) evidence supports the use of conventional immunosuppressive agents for those failing IVIG, prednisone, or plasma exchange. Neither azathioprine, cyclosporine, methotrexate, cyclophosphamide, nor mycophenolate mofetil are of proven efficacy in such patients. Various biologic agents may be useful, but hard data are not yet available.

Natalizumab, a monoclonal antibody directed against integrin subunits on the surface of activated T cells, is under consideration for therapeutic trial in CIDP. In a single case report, it proved ineffective. Rituximab, a monoclonal antibody directed against the B-cell surface antigen CD20,

Stroke Alert: A Review of Current Clinical Stroke Literature

Environmental and Lifestyle Impact on Stroke Risk

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

Editor's Note: This series of well-designed epidemiological studies emphasizes the importance of diet, sunlight exposure, stress, and vitamin deficiencies in the pathogenesis and risk of stroke.

Mediterranean Diet Can Reduce Risk for Stroke

Source: Estruch R, et al, for the PREDIMED Study Investigators. Primary prevention of cardiovascular disease with a Mediterranean diet. *N Engl J Med* 2013; Feb. 25. DOI: 10.1056/NEJMoa1200303. [Epub ahead of print].

The PREDIMED investigators from Barcelona, Spain, reported the results of their multicenter, randomized dietary treatment trial of the effects of three different diets on cardiovascular events — a Mediterranean diet supplemented with extra virgin olive oil, a Mediterranean diet supplemented with mixed nuts, or a control diet that included advice to reduce dietary fat. The Mediterranean diet is characterized by a high intake of olive oil, fruit, nuts, vegetables, and cereals; a moderate intake of fish and poultry; a low intake of dairy products, red meat, processed meats, and sweets; and wine in moderation consumed with meals. A number of observational cohort studies suggested that this diet, over many years, might confer a reduced risk of cardiovascular disease, but this was the first large-scale, randomized study that directly compared diets. The primary endpoint was the rate of major cardiovascular diseases (myocardial infarction, stroke, death from cardiovascular causes), and the trial was stopped early (median follow-up of 4.8 years) when an interim analysis showed a significant difference in outcomes, based on which diet was instituted.

The enrolled subjects were free of cardiovascular disease, but had risk factors for disease — type 2 diabetes mellitus, or at least three of the following other risk factors: smoking, hypertension, elevated LDL, low HDL, obesity, or family history of premature coronary heart disease. A total of 7447 patients were enrolled (ages 55 to 80 years); 57% were women, and they were followed for a mean time of 4.8 years before the study was terminated. In a multivariable-adjusted analysis, the hazard ratios were 0.70 (95% confidence interval [CI], 0.54-0.92) for the Mediterranean diet with extra olive oil, and 0.72 (95% CI, 0.54-0.96) for the group assigned to the Mediterranean diet with nuts, vs the control group. For stroke alone, the hazard ratios for the two Mediterranean diets were 0.67 (olive oil) and 0.54 (nuts). Adherence to the Mediterranean diet results in a clinically and statistically significant reduction in cardiovascular events, especially stroke. ■

Low Levels of Light Exposure Associated with Higher Stroke Incidence

Source: Kent ST, et al. Short- and long-term sunlight radiation and stroke incidence. *Ann Neurol* 2013;73:32-37.

This investigation was a subset observational cohort of the REGARDS trial, which looked at a variety of risk exposures to African American and white patients living in the Southeastern Stroke Belt as well as the Southwest United States. Sunlight exposure was determined by using the North American Land Data Assimilation System dataset with calculation made for different regions over periods of 15-, 10-, 5-, 2-, and 1-year exposures. A cohort of 16,606 stroke and coronary artery disease-free black and white participants > 45 years were analyzed for these defined time periods, and compared for stroke risk using the lowest and highest quartiles of exposure to sunlight. After adjustment for other covariates, the previous year's monthly average insolation exposure that was below the median gave a hazard ratio of 1.61 (95% CI, 1.15-2.26) and the previous year's highest monthly average temperature exposure gave an HR of 1.92 (95% CI, 1.27-2.92).

The results of this study suggest that low light exposure increases stroke risk and that high temperature exposure increases stroke risk. The physiologic mechanisms related to these observations are unknown and require further investigation. ■

Psychosocial Stress Increases Risk of Stroke in Older Adults

Source: Henderson KM, et al. Psychosocial distress and stroke risk in older adults. *Stroke* 2013;44:367-372.

THE INVESTIGATORS REPORTED DATA FROM THE CHICAGO Health and Aging Project, a longitudinal population-based study of community-dwelling black and non-Hispanic white adults, aged 65 years or older, living on the south side of Chicago. Psychosocial distress was measured from an analytically derived composite measure of depressive symptoms, perceived stress, neuroticism, and life dissatisfaction. A total of 6769 people were included and followed in this study. Cox proportional hazards ratio model was used to examine the association of distress with stroke incidence and mortality over a 6-year follow-up period.

The authors identified 151 stroke deaths and 452 incident strokes. After adjusting for age, race, and sex, the hazard ratio for each 1-standard deviation increase in distress was 1.47 (95% CI, 1.28-1.70) for stroke mortality and 1.18 (95% CI, 1.07-1.30) for incident stroke. Secondary analysis showed that distress was strongly related to hemorrhagic stroke (hazard ratio [HR],1.70) and not with ischemic stroke (HR, 1.02). In conclusion, the investigators stated that increasing levels of psychosocial distress are associated with an excess risk of stroke in older adults. The physiological mechanisms that underly this association (i.e., hypertension, cardiac arrhythmias, etc.) remain to be elucidated. ■

Vitamin D Deficiency May Increase Risk of Ischemic Stroke

Source: Brondum-Jacobsen P, et al. 25-hydroxyvitamin D and symptomatic ischemic stroke: An original study and meta-analysis. *Ann Neurol* 2013;73:38-47.

AS PART OF THE COPENHAGEN CITY HEART STUDY, INvestigators measured plasma 25-hydroxyvitamin D in 10,170 individuals from the general population, and followed them for 21 years. During the follow-up period, 1256 developed ischemic strokes and 164 persons developed hemorrhagic strokes. A stepwise decrease in vitamin D levels was accompanied by a stepwide increase in the risk of ischemic stroke, and this varied by seasonal adjustments.

Using a Cox regression model comparing individuals with plasma vitamin D levels between the 1st and 4th percentiles to individuals with vitamin D concentrations between the 50th and 100th percentiles, the adjusted hazard ratio for ischemic stroke was 1.82 (95% CI, 1.41-2.34). Vitamin D levels were not associated with risk of hemorrhagic stroke. In a multivariate adjusted odds ratio of a meta-analysis of 10 other studies that examined vitamin D levels and stroke, comparing the lowest quartile with the highest quartile, the adjusted odds ratio for ischemic stroke was 1.54. This study confirms many others that vitamin D deficiency may increase the risk of ischemic stroke. ■

has had conflicting results but may be an option in otherwise refractory CIDP. Alemtuzumab, a recombinant DNA-derived humanized monoclonal antibody directed against the cell surface glycoprotein CD52 on the surface of most B and T lymphocytes, has had variable success, but secondary autoimmunity developed in several patients. Eculizumab, a monoclonal antibody that inhibits the production of terminal complement component C5a and membrane attack complex C5b-9 by binding to complement protein C5, has not yet been offered in CIDP but was deemed safe in 13 patients with multifocal motor neuropathy.[1] ■

Reference

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Adult Seizures and Social Outcomes of Children with Partial Complex Seizures

ABSTRACT & COMMENTARY

By Nitin K. Sethi, MD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *Early and aggressive treatment of seizures, educational and social habilitation, as well as treatment of psychiatric comorbidities is advisable in intellectually normal children with focal epilepsy*

(partial complex seizures with or without secondary generalization).

Source: Camfield CS, Camfield PR. The adult seizure and social outcomes of children with partial complex seizures. *Brain* 2013;136(Pt 2):593-600.

Focal epilepsy (partial complex seizures or focal with secondary generalized seizures) is common in children. Intellectually normal children with focal epilepsy usually evade characterization into a specific epilepsy syndrome apart from those with benign Rolandic and benign occipital epilepsies. Long-term follow-up of these children with partial complex seizures but normal intelligence reveals that many fail to achieve adequate seizure control and remission with anticonvulsant therapy as compared to those children with only secondary generalized seizures. Long-term social outcome is also poor with a high prevalence of learning disorders, restricted social relationships (more likely to be single, unmarried, or living alone), poor socioeconomic status, lower educational status attained, and psychiatric comorbidities.

The authors investigated seizure and social outcomes in intellectually normal children with focal epilepsy when they grow up as adults. Cases were identified from the population-based Nova Scotia Childhood epilepsy cohort (1977 through 1985) and two groups were defined: those with solely secondary generalized seizures (SecGen seizures) and those with partial seizures with or without secondary generalized seizures (PCS) based on centralized EEG recordings with the diagnosis confirmed by chart review and personal interview. The patients and their parents, when possible, were interviewed by the authors by telephone between 2009 and 2012. Patients with PCS were likely to have more severe epilepsy, be on polypharmacy (> 2 antiepileptic drugs), and experience less frequent remissions as compared to the SecGen seizure group. Emotional and behavioral outcomes were unfavorable in both the groups with a higher prevalence of restricted social relationships, behavioral problems, and psychiatric diagnoses (other than attention deficit/hyperactivity disorder) in PCS as compared to the SecGen group. The authors recommend early and aggressive treatment of focal seizures, and educational and social rehabilitation in these intellectually normal children to improve their quality of life.

■ COMMENTARY

Previous studies have yielded conflicting results in children with focal epilepsy, with some showing a good outcome (social and economic independence) while others showed continued seizures, especially in patients with structural lesions on MRI and unsatisfactory social, behavioral, and psychiatric outcomes.[1,2] Future studies combining video-EEG characterization of epilepsy type (frontal vs temporal lobe) and seizure control, presence or absence of MRI lesion, and detailed neuropsychological testing shall yield more useful information. Studies investigating whether intensive and aggressive treatment of seizures, social, educational, and behavioral habilitation of these children at a young age improves outcome are also direly needed. ■

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Medial Thalamic Dysregulation in Idiopathic Restless Legs Syndrome

ABSTRACT & COMMENTARY

By Alexander Shtilbans, MD, PhD

Assistant Professor of Neurology, Weill Cornell Medical College

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

Synopsis: *There is a reduced N-acetylaspartate/creatine-phosphocreatine ratio and N-acetylaspartate concentration at the level of the medial thalamus in patients with restless legs syndrome (RLS), suggesting involvement of the limbic system in the pathophysiology of RLS.*

Source: Rizzo G, et al. Abnormal medial thalamic metabolism in patients with idiopathic restless legs syndrome. *Brain* 2012;135:3712-3720.

Restless legs syndrome (RLS) is a sensorimotor disorder characterized by a distressing urge to move the legs and occasionally the arms, usually accompanied by uncomfortable sensations in the affected limbs. The sensations occur particularly in the evening or at night and are relieved by movement. RLS can be primary or secondary due to metabolic abnormalities. The pathophysiology of primary RLS is poorly understood. A previously published functional MRI (fMRI) study[1] revealed activation in the medial thalamus, putamen, middle frontal gyrus, and anterior cingulated gyrus in patients with RLS, implicating limbic system involvement.

The authors of this paper evaluated the metabolism and structural features of medial thalamic regions in patients with idiopathic RLS using multimodal MRI tests, which included proton magnetic resonance spectroscopy (H-MRS), diffusion tensor imaging, voxel-based morphology as well as volumetric and shape analysis. This was a cross-sectional study in which 23 patients with chronic idiopathic RLS and 19 healthy controls were studied. The patient group was comprised of drug-naïve patients as well as those treated with dopaminergic medications. The latter were off of their medications for at least 2 weeks prior to the study. The H-MRS study revealed a significantly reduced N-acetylaspartate/creatine-phosphocreatine ratio and N-acetylaspartate concentration at the level of the medial thalamus in patients with RLS. Interestingly, the lower N-acetylaspartate levels were associated with a family history of RLS in the studied patients. Volumetric and shape analysis, however, showed no difference between patients and controls. The reduced levels of N-acetylaspartate were similar in both previously treated and untreated RLS patients. No other magnetic resonance modality showed any differences between the patients and controls in the study. Based on the observed results, the authors suggested that the involvement of the medial portion of the thalamus could have a primary role in the pathophysiology of RLS because its function is modulated by dopaminergic afferents. It is also suggested that given a role of medial thalamus in sleep regulation, the observed decrease in N-acetylaspartate could be secondary to the sleep impairment. Furthermore, dopaminergic dysfunction may impair medial thalamic pain processing, implicating the endogenous opioid system in the pathogenesis of RLS. The authors concluded that the observed abnormal medial thalamic metabolism in RLS suggests a role of limbic system pathology in this disease.

■ COMMENTARY

Previous fMRI studies showed activation of thalamus and anterior cingulated gyrus among other brain areas in patients with RLS. The authors of the current study evaluated metabolism and structural features of medial thalamic regions of the RLS patients compared to healthy controls. The study design shows slight predominance of women in the study group compared to controls. The patients were off of dopaminergic medications for at least 2 weeks prior to the study. It is not clear, however, if a 2-week washout period would be sufficient to completely eliminate the effect of these medications. The authors do not mention any medications that the controls might have been taking for any non-neurological conditions, which could be a confounder. Additionally, it is not clear whether other diseases potentially affecting the findings in either patients or controls have been excluded.

The reduction in N-acetylaspartate observed in the patient group was the only difference noted in the study, which utilized several imaging modalities such as diffusion tensor imaging, voxel-based morphometry, and volumetric and shape analysis. N-acetylaspartate is thought to be a neuronal marker, which previously was noted to be decreased in neurodegenerative conditions such as amyotrophic lateral sclerosis and multiple sclerosis. The decrease in such a marker could represent either neuronal loss or neuron dysfunction, the latter being more likely given that there are no structural differences noted between the groups. The authors suggest that the involvement of the medial portion of the thalamus might play a primary role in the disease and reflects an impairment of medial pain mechanism secondary to dopaminergic dysfunction.

The authors only used idiopathic RLS patients in this study, but it would be interesting to see if other forms of RLS, such as those related to pregnancy, iron deficiency, or renal impairment, would be also associated with decreased N-acetylaspartate in the medial thalamus. The authors acknowledged a limitation of the study related to lack of investigation of circadian changes in patients with RLS. But overall, the authors present important findings that could shine light on the pathophysiology of idiopathic

RLS and hopefully broaden our knowledge of brain areas affected by this disease. ■

Reference

1. Astrakas LG, et al. T2 relaxometry and fMRI of the brain in late-onset restless legs syndrome. *Neurology* 2008;71:911-916.

CME Objectives

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

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

CME Instructions

To earn credit for this activity, follow these instructions:

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

CME Questions

1. Which of the following is *not* true regarding brain stimulation?
a. Low-dose direct current transcranial stimulation (tDCS) of the brain is safe.
b. tDCS has been shown to improve motor performance in healthy elderly subjects.
c. Transcranial magnetic stimulation is approved for use in the treatment of medication-resistant depression.
d. A deep brain stimulation trial of the fornix is underway for the treatment of Alzheimer's disease.
e. All of the above

2. Childhood chronic inflammatory demyelinating polyradiculoneuropathy:
a. responds to intravenous immunoglobulin.
b. affects males and females equally.
c. most often presents with disease progression spanning more than 8 weeks.
d. most often have a relapsing, rather than a monophasic, course.
e. All of the above are true

3. Which statement regarding seizure, social, and behavioral outcomes of children with partial complex seizures (PCS) is true?
a. Intellectually normal children with PCS have good adult seizure control and no social and behavioral problems.
b. Emotional and behavioral outcomes are no different in intellectually normal children with partial complex seizures as compared to those with solely secondary generalized seizures.
c. Early and aggressive treatment of seizures as well as early social, behavioral, and educational habilitation is recommended for intellectually normal children with partial complex seizures.
d. Intellectually normal children with partial complex seizures do not need social, behavioral, and educational habilitation.

4. Restless legs syndrome is associated all of the following conditions *except*:
a. coronary artery disease.
b. chronic renal insufficiency.
c. iron deficiency.
d. pregnancy.

5. Careful adherence to the Mediterranean diet over many years can reduce the risk of stroke and heart attack.
a. True
b. False

6. Severe stress has no effect on the development of cardiovascular diseases.
a. True
b. False

7. Absence of exposure to natural sunlight may increase the risk of ischemic stroke.
a. True
b. False

8. 25-hydroxyvitamin D deficiency is associated with an increased risk of stroke.
a. True
b. False

In Future Issues:

Update on Gulf War Syndrome

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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A Relationship Between Nocturia and Hypertension

Source: Feldstein CA. *J Am Soc Hypertens* 2013;7:75-84.

Nocturia could easily be misconstrued as a "nuisance" symptom since, after all, nobody dies from nocturia … or do they? Indeed, urinary frequency and nocturia have been associated with greater risk for nocturnal falls and hip fracture; hence, nocturia can be much more than just a nuisance.

Clinicians are used to identifying nocturia as a symptom associated with benign prostatic hyperplasia, overactive bladder, uncontrolled diabetes, uncontrolled congestive heart failure, use of diuretics, and (less commonly) interstitial cystitis. What is only minimally recognized, however, is the emerging observation that hypertension is associated with nocturia.

Several plausible mechanisms can explain the nocturia/hypertension relationship: hypertension-induced alterations in glomerular filtration or tubular transport, activation of atrial natriuretic peptide from ventricular wall stress induced by hypertension, and resetting of the pressure-natriuresis relationship in the kidney, to name a few.

Feldstein indicates that the prevalence of nocturia in untreated hypertension patients may be as high as 33%. Since nocturia can be both a burdensome symptom and lead to significant morbidity (and mortality), clinicians may wish to specifically inquire about nocturia when encountering hypertension patients. ■

Peripheral Artery Disease: Helping Patients to Walk the Walk

Source: Ahimastos AA, et al. *JAMA* 2013; 309:453-460.

Currently available treatments for peripheral artery disease (PAD) are only modestly effective. PAD portends increased risk of cardiovascular disease; hence, most PAD patients should be receiving pharmacotherapy with a statin and an antiplatelet agent (usually clopidogrel).

Because one of the quality-of-life limiting factors in advanced PAD is disease-mediated diminution in walking distance and walking time, incorporation of pharmacotherapy to improve these limitations is also considered important. Unfortunately, the two FDA-approved treatments (pentoxifylline and cilostazol) for symptoms of PAD provide only a modest increase in walking distance (25% or less). Smoking cessation and exercise advice remain critically important, but are too often not heeded.

Ramipril is an angiotensin-converting enzyme (ACE) inhibitor that has been used in numerous major clinical trials, including the HOPE trial, ONTARGET trial, REIN trial, and others. Use of ramipril is usually predicated on 1) its ability to lower blood pressure, 2) its ability to improve outcomes in congestive heart failure, or 3) its ability to improve albuminuria.

Based on results seen in a small pilot trial that suggested favorable results of ramipril on treadmill time in subjects with PAD, Ahimastos et al performed a larger randomized clinical trial (n = 212).

At the conclusion of the 6-month trial of ramipril 10 mg/day vs placebo, pain-free walking time had increased by more than 50% in the ramipril group, but only 10% in the placebo group.

Although the mechanism for improved function is speculative, it has been noted that ACE inhibitors increase skeletal muscle blood flow; indeed, this has been the mechanism to which improved insulin sensitivity in diabetics has been attributed. Ramipril may offer a new avenue to improve functionality in patients with PAD. ■

Long-Term Functional Outcomes After Localized Prostate Cancer Treatment

Source: Resnick MJ, et al. *N Engl J Med* 2013;368:436-445.

When prostate cancer is localized, either radical prostatectomy (RPT) or external beam radiation (EBR) can often be curative. The adverse effect profile of these two interventions, however, may be meaningfully different and such differences might also be time-dependent.

Resnick et al studied men (n = 1164) from the Prostate Cancer Outcomes Study who had been enrolled between the ages of 55-74 and had localized prostate cancer. More than 80% of the men had a Gleason score of 7 or less. The prevalence of urinary incontinence (UI) and erectile dysfunction (ED) were compared among these men at years 2, 5, and 15.

Prostatectomy subjects were five to six times more likely to have incontinence at

2 years and 5 years than EBR subjects. Similar disadvantage was seen in the prevalence of ED (two- to four-fold increased incidence in the RPT group). At the 15-year conclusion of their observations, no differences between groups remained. However, one would anticipate, for instance, a substantial incremental increase in ED as men age *with or without intervention*; hence, the fact that between-group differences are eliminated by 15 years provides little solace for the men who suffer the adverse effects in the interim! ■

The Word 'GPR40 Modulator' May Soon be Entering Our Vocabulary

Source: Basu A, et al. *Diabetes Care* 2013;36:185-187.

The search for safe and effective agents to treat type 2 diabetes (DM2) continues, with hypoglycemia often being a limiting adverse effect of otherwise highly efficacious agents.

It has been observed that free fatty acids (FFA) play a role in glucose homeostasis, although the story line is complex. Acutely, elevations of FFA *stimulate* beta cell secretion of insulin. *Chronic* FFA elevations result in an impaired insulin response to high glucose levels, a phenomenon known as lipotoxicity.

The mechanism by which FFA impacts insulin secretion has been elegantly worked out and includes the G-protein-coupled receptor (GPR40). Because GPR is involved not only in insulin secretion, but also plays a role in obesity and dyslipidemia, its potential as a multimodal intervention has looked promising.

Studies in humans have shown that GPR40 agonists live up to the expectation that they lower glucose, with a very low risk of hypoglycemia. For instance, a head-to-head comparison with the sulfonylurea glimepiride found hypoglycemic episodes to be six-fold lower with the GRP40 agonist.

In an era of a burgeoning population of DM2 patients, we look forward to the addition of pharmacotherapies that safely complement our current options. ■

A More Effective Regimen for *H. pylori* Eradication

Source: Liou JM, et al. *Lancet* 2013;381: 205-213.

In the United States, peptic ulcer disease is caused primarily by two culprits: nonsteroidal anti-inflammatory drugs and *Helicobacter pylori* (and their combination). Evolution of pharmacotherapy for *H. pylori* currently employs combinations of amoxicillin (AMOX), metronidazole (METR), clarithromycin (CLAR), and a proton pump inhibitor (PPI). Unfortunately, over time *H. pylori* eradication rates with such regimens have fallen to as low as 80% or less. Is there a better way?

Liou at al randomized *H. pylori*-positive Taiwanese adults (n = 900) to one of three regimens — 1) Sequential 10 days: PPI + AMOX for 5 days followed by PPI + CLAR + METR for 5 days; 2) Sequential 14 days: PPI + AMOX for 7 days followed by PPI + CLAR + METR for 7 days; or 3) Standard 14 days: PPI + AMOX + CLAR for 14 days. The PPI used in this clinical trial was lansoprazole.

Adverse effect profiles of the three regimens were similar. Eradication rates were statistically significantly higher using sequential regimens (10 days = 87%, 14 days = 91%) than in standard regimens (82%).

Reflecting an increased recognition of problematic CLAR resistance at the end of the initial comparison trial, treatment failures from each regimen were assigned to receive an additional 14-day sequential course of treatment in which levofloxacin was substituted for CLAR. Eradication rates from this "rescue" population (regardless of which initial regimen they had received) were 80%.

Based on this large dataset, the authors suggest that sequential treatment regimens should become first line. ■

Uric Acid: How Much of a Bad Guy?

Source: Rosendorff C, et al. *J Clin Hypertens* 2013;15:5-6.

Uric acid (URA) has become the object of intense scrutiny of late, with more than its share of accusations linking it to hypertension and heart disease. The relationship between URA and gout is incontrovertible, though not necessarily universal. That is, in persons who develop gout, risk of future attacks is definitely related to absolute URA plasma levels. However, among persons without gout, elevations of URA appear to be well tolerated without evident toxicity in most: In asymptomatic adults with URA levels > 9.0 mg/dL, only about 5% per year go on to manifest acute gout.

The association of URA with hypertension, myocardial infarction, and even congestive heart failure is acknowledged. Whether this relationship is *causal*, and if a causal relationship is determined, whether lowering of URA will be beneficial remains to be determined. Remember the enthusiasm attendant to the recognition that homocysteine was associated with cardiovascular disease, heightened by the assurance that lowering homocysteine was simple and safe (B vitamins and folate), soon thereafter torpedoed by the interventional trials that failed to show improved outcomes in subjects whose homocysteine levels were reduced?

Despite the growing enthusiasm for criminalizing URA, we still do not have a large randomized, controlled trial indicating that modulation of URA improves hard endpoints. Until then, since all medications that reduce URA have their own bundle of potential misadventure to consider, we should watch and wait. ■

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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.*

Is This the End of the Road for Calcium Supplementation?

In this issue: Calcium supplementation in women; type 2 diabetes treatments and pancreatitis risk; treating chronic idiopathic urticaria; rivaroxaban and VTE; and FDA actions.

High calcium intakes in women

Another study suggests that calcium supplementation may lead to excess all-cause mortality and cardiovascular disease in otherwise healthy women. Researchers studied more than 61,000 Swedish women for 19 years. Diet and calcium intake, including calcium supplementation, were assessed with the primary outcome being death from all causes and cause-specific cardiovascular disease, ischemic heart disease, and stroke. Higher *dietary* intake of calcium (> 1400 mg/day) was associated with a higher death rate from all causes compared to intake between 600-1000 mg/day (hazard ratio [HR], 1.40; 95% confidence interval [CI], 1.17-1.67). Higher calcium intake was also linked to increased risk of cardiovascular disease (HR, 1.49; CI, 1.09-2.02) and ischemic heart disease (HR, 2.14; CI, 1.48-3.09). There was no higher risk of stroke. Intake of calcium in tablet form > 1400 mg/day was associated with 2.5 times greater risk of death from all causes (HR, 2.57; CI, 1.19-5.55). The authors conclude that higher intakes of calcium in women are associated with higher death rates from all causes as well as increased rates of cardiovascular disease but not stroke (*BMJ* published online Feb. 13, 2013. DOI: org/10.1136/bmj.f228). Previous studies have focused more on stroke risk associated with calcium showing mixed results. This well-done study, along with previously published data from the Women's Health Initiative, provides ample evidence to rethink calcium supplementation for the 60% of middle-aged and older American women who are regular users of calcium supplements. The U.S. Preventive Services Task Force came to the same conclusion (even before this study was published) with publication of updated guidelines in February stating that "current evidence is insufficient to assess the balance of the benefits and harms of combined vitamin D and calcium supplements for the primary prevention of fractures in postmenopausal women or men." They further state there is no evidence to support use of more than 1000 mg of calcium and 400 mcg of vitamin D per day and recommends against using doses lower than 1000 mg of calcium and 400 mcg of vitamin D. Their rationale is that supplementation does not reduce fracture risk but does increase the risk of renal stones in otherwise healthy women. This does not apply to women with osteoporosis or vitamin D deficiency (*Ann Intern Med*, published online Feb. 26, 2013). ■

Diabetes therapies and pancreatitis risk

Glucagonlike peptide 1 (GLP-1) mimetics (e.g., analogs of GLP-1 and dipeptidyl peptidase IV inhibitors) used for the treatment of type 2 diabetes might increase the risk of pancreatitis, according to a recent population-based, case-control study. Using a large population database of

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type 2 diabetics, 1269 cases of acute pancreatitis were identified and those patients were matched with 1269 controls with similar risk factors (age, sex, diabetes mellitus complications, etc). After adjusting for available confounders, current use of GLP-1 based therapies (exenatide [Byetta] and sitagliptin [Januvia]) more than doubled the risk for acute pancreatitis (adjusted odds ratio 2.24, 95% CI, 1.36-3.68). The authors state that "Our findings suggest a significantly increased risk of hospitalization for acute pancreatitis associated with the use of sitagliptin or exenatide among adult patients with type 2 diabetes mellitus" (*JAMA Intern Med* published online Feb. 25, 2013. DOI: 10.1001/jamainternmed.2013.2720). Both drugs already carry a boxed warning regarding pancreatitis. ■

Omalizumab for idiopathic urticaria

Chronic idiopathic urticaria is one of the most frustrating entities to treat as many patients do not respond to antihistamines, even in high doses. Now, a new study suggests that omalizumab (Xolair), an IgE monoclonal antibody used to treat asthma, may be effective in these patients. Patients with moderate-to-severe chronic idiopathic urticaria (n = 323) were randomized to SQ injections of omalizumab every 4 weeks for three total injections at doses of 75 mg, 150 mg, 300 mg, or placebo. The primary outcome was itch-severity score. The 75 mg dose was no better than placebo, but the two higher doses showed significant reductions in itching, with the 300 mg dose being the most effective. The higher dose was also associated with the highest risk of side effects, however, at about 6%. The authors conclude that omalizumab was effective in these patients who were previously symptomatic despite antihistamines. The study was sponsored by the drug manufacturers Genentech and Novartis Pharma (*N Engl J Med* published online Feb. 24, 2013. DOI: 10.1056/NEJMoa1215372). ■

Rivaroxaban for VTE prevention

Rivaroxaban, the oral Xa inhibitor, is as effective as enoxaparin in preventing venous thromboembolism (VTE) in patients with acute medical illnesses, but with a higher risk of bleeding, according to a new study. More than 8100 acutely ill hospitalized patients were randomized to 10 days of enoxaparin 40 mg SQ daily or 35 days of rivaroxaban 40 mg orally with matching placebos. The primary outcome of asymptomatic or symptomatic VTE occurred in 2.7% of patients in both groups by day 10. By day 35, the rates were 4.4% for rivaroxaban and 5.7% for enoxaparin ($P = 0.02$). However, the bleeding rate was more than double in the rivaroxaban group at day 10 (2.8% vs 1.2%, $P < 0.001$) and even higher at day 35 (4.1% vs 1.7%, $P < 0.001$). The authors conclude that rivaroxaban was noninferior to enoxaparin for standard duration thromboprophylaxis (10 days) and reduced the risk of VTE at 35 days with an increased risk of bleeding (*N Engl J Med* 2013;368:513-523). ■

FDA actions

A new selective estrogen receptor modulator (SERM) has been approved for the treatment of dyspareunia due to vulvar and vaginal atrophy in postmenopausal women. Ospemifene appears to benefit vaginal epithelium without significant effect on the endometrium. The drug's safety and efficacy was established in three clinical trials of nearly 1900 postmenopausal women with vulvar and vaginal atrophy who were randomly assigned to ospemifene or placebo. After 12 weeks, the first two trials showed statistically significant improvement in dyspareunia while the third trial supported the long-term safety of the drug. The drug is contraindicated in women with genital bleeding, estrogen-dependent cancer, or thromboembolic disease. The risk of stroke and VTE was higher than baseline but lower than the rates seen with estrogen replacement therapy. Ospemifene comes with a boxed warning regarding endometrial hyperplasia and abnormal vaginal bleeding. Common side effects include hot flashes, vaginal discharge, muscle spasms, and sweating. It will be marketed by Shionogi Inc. as Osphena.

The FDA has approved ado-trastuzumab emtansine for use as a single agent in patients with late-stage, HER2-positive breast cancer. The drug is approved for patients who have already been treated with trastuzumab and taxane separately or in combination. Approval was based on a study of nearly 1000 women with metastatic breast cancer in which progression-free survival was about 3 months longer with the drug compared to lapatinib plus capecitabine, and overall survival was about 6 months longer. Ado-trastuzumab emtansine is marketed by Genentech as Kadcyla. ■