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INSIDE

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Pesticides and Parkinson's Disease

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

Assistant Professor, Neurology and Neuroscience, Weill Cornell Medical College

Dr. Nirenberg reports that she has participated in consulting for Biovail and clinical research trials sponsored by Boehringer-Ingleheim.

Synopsis: *Elevated levels of a specific organochlorine pesticide are associated with Parkinson's disease.*

Source: Richardson J R, Shalat SL, Buckley B, et al. Elevated serum pesticide levels and risk of Parkinson Disease. *Arch Neurol* 2009;66: 870-875.

EPIDEMIOLOGICAL STUDIES HAVE IMPLICATED PESTICIDES AS A possible environmental cause for Parkinson's disease (PD), but little is known about the specific toxins that may be to blame. Organochlorine pesticides are potential candidates, because they are lipophilic, highly persistent in the environment, and neurotoxic to dopaminergic neurons in rodent models. High levels of specific organochlorine pesticides have also been identified in the postmortem brains of PD patients.

In this study, the authors used a case-control study design to test the hypothesis that high serum levels of specific organochlorine pesticide(s) are associated with PD. They examined blood samples from subjects with PD (n=50) at a tertiary movement disorders center, and compared them with those of subjects with Alzheimer's disease (AD) (n=20), and healthy controls (n=43). They then used gas chromatography-mass spectrometry to test the samples for the presence of 16 different organochlorine pesticides, restricting further analysis to pesticides that were detected in at least half of the subjects with PD.

The pesticide that was most commonly detected in the serum of PD patients was ß-hexachlorocyclohexane (ß-HCH), which

was present in 38/50 (76%) of PD patients, compared with 17/43 (40%) of healthy controls and 6/20 (30%) AD patients. The median level of ß-HCH was also significantly higher in subjects with PD (0.36 ng/mL) than in either control subjects (0 ng/mL) or subjects with AD (0 ng/mL). The findings raise the possibility that ß-HCH may play a role in the pathogenesis of PD.

■ COMMENTARY

In spite of the rapidly growing literature about the genetic basis for PD, there remains a paucity of information about potential environmental PD risk factors. Such environmental factors may be sufficient to cause disease, or may account for the known differences in phenotype (or penetrance) between carriers of the same gene mutation.

In this study, the authors demonstrate that the presence of ß-HCH is associated with a clinical diagnosis of PD, suggesting that this organochlorine pesticide may cause or increase vulnerability to PD. Study strengths include the use of two different comparison groups — both healthy controls and subjects with AD — to exclude a non-specific association of this pesticide with neurodegenerative disorders. Limitations include the small sample size and homogeneous study sample, such that the findings may not be generalizable to other populations. Subjects in the AD group were also significantly older than the PD subjects, and thus may not have been an appropriate comparison group.

Based on the authors' findings, larger, prospective studies are warranted to clarify the potential role of ß-HCH in conferring risk for PD. Identification of environmental risk factors for PD is critical from a public health perspective, and may also provide new insights into the pathogenesis of the disease. ■

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Rituximab for Neuropathy with IgM Monoclonal Gammopathy

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *In preliminary, open-label trials, rituximab shows promise as a treatment for IgM-associated neuropathy.*

Source: Niermeijer JMF, Eurelings M, Lokhorst HL, et al. Rituximab for polyneuropathy with IgM monoclonal gammopathy. *J Neurol Neurosurg Psychiatry* 2009;80; 1036-1039

Among 17 patients with progressive or disabling polyneuropathy and IgM monoclonal gammopathy, encompassing three women and 14 men, intravenous rituximab 375 mg/m^2 was administered in an open-label trial once weekly for four weeks, with subsequent follow-up for a median of 12 months. Age of onset ranged from 44 years to 67 years (median 55 years), duration from two years to 14 years (median seven years), and all but one had demyelinating, rather than axonal, polyneuropathy. Previous treatments in five patients included intermittent combined cyclophosphamide and prednisone, with fludarabine added in two. Electrodiagnostic studies were performed prior to and nine months following treatment initiation. Improvement of the Overall Disability Sum Score (ODSS) by one or more points was the primary outcome measure. Secondary outcome measures included improvement of the Modified Rankin Scale (MRS) by one or more

points, distal MRC (motor) or sensory sum score improvement by 5% or more, nerve conduction velocity improvement, drop in M protein concentration, or disappearance of CD20-positive B cells in bone marrow, and adverse events. Statistical analysis included the Wilcoxon matched pairs test, the Mann-Whitney U test, and the X^2 test, with $p < 0.05$ considered statistically significant.

Rituximab resulted in improved sensory sum score in 9/17 patients, improved MRS in 5/17 patients, improved MRC (motor) sum score in 4/17 patients, and improved ODSS in two patients. CD20-positive B cells were depleted in the bone marrow in all patients and median IgM concentration significantly decreased following treatment. Nerve conduction velocities improved by 10% or more in 4/17 patients in two or more nerves, and in 2/17 patients in a single nerve. No serious adverse events were recorded during the study period. Rituximab response rate in polyneuropathy with IgM monoclonal gammopathy is comparable to that seen with combined cyclophosphamide and prednisone or fludarabine, and warrants further investigation in controlled clinical trials.

■ **COMMENTARY**

Rituximab, a chimeric monoclonal antibody against the CD20 protein on B-lymphocytes, is beneficial against a host of diseases, including autoimmune disorders (rheumatoid arthritis, idiopathic thrombocytopenic purpura, myasthenia gravis), lymphoma, and leukemia. Lambert-Eaton myasthenic syndrome (LEMS) may soon be added to the list. (*See* Pellkofer HL, Voltz R, Kuempfel T. Favorable response to rituximab in a patient with anti-VGCC-positive Lambert-Eaton myasthenic syndrome and cerebellar dysfunction. *Muscle Nerve* 2009;40;305-308).

In this case report, a 61-year-old-man was wheelchair bound after a five-year history of coincident non-paraneoplastic Lambert-Eaton myasthenic syndrome and subacute severe cerebellar degeneration. Rituximab administration resulted in symptomatic improvement following poor response to intravenous immunoglobulin infusion, steroids, azathioprine, and plasma exchange. Dysarthria and dysphagia abated and he was able to ambulate 200 m to 300 m without assistance. With worsening of symptoms and reappearance of B cells, improvement was recaptured with depletion of B cells following repeat rituximab infusions. Well-tolerated and safe, rituximab may be a therapeutic option for LEMS when other treatments fail. ■

TMS as an Adjunct to Rehabilitation After Stroke: A Potential New Treatment

ABSTRACT & COMMENTARY

By Bruce T. Volpe, MD

Professor of Neurology and Neuroscience, Department of Neurology, Weill Cornell Medical College and the Burke Rehabilitation Hospital.

Dr. Volpe reports that he receives grant/research support from Wyeth/Pfizer.

Synopsis: *Transcranial magnetic stimulation was shown to have benefit during stroke rehabilitation therapy, in this randomized, controlled clinical trial.*

Source: Khedr EM, Etraby AE, Hemeda M, et. al. Long-term effect of repetitive transcranial magnetic stimulation on motor function recovery after acute ischemic stroke. *Acta Neurol Scand*, August 2008 (E-pub ahead of print). DOI: 10.1111/j.1600-0404.2009.01195.x.

THIS RESEARCH GROUP, FROM ASSIUT, EGYPT, TESTED whether the application of repetitive transcranial magnetic stimulation (rTMS) to the skull area over the affected hemisphere would improve motor outcome and reduce disability in patients with stroke. This was an ambitious "pilot study" to generate important information about a number of trial-specific features that includes aspects of a phase 1 study (safety of increasing intensity and frequency of rTMS), a phase 2 study (effectiveness for a specific motor outcome), and a phase 3 study (controlled trial).

The investigators randomly assigned 48 patients with acute ischemic stroke to receive either sham rTMS or rTMS at one of two frequencies (3Hz or 10Hz). Sham rTMS or rTMS was delivered over the affected hemisphere daily for five days. All patients received the same medical treatment (low molecular weight heparin in the first week, then aspirin and piracetam, 2–4g/d, chronically). They also received post-stroke rehabilitation consisting of early passive motion that was later modified to more active treatment. They measured motor performance in the upper and lower limb, the National Institutes of Health (NIH) stroke scale, and the Modified Rankin Scale, before and after treatment and again one month, two months, three months, and 12 months later. Demo-

graphics, including age (59.5 ± 13), gender (24M/24F), time from stroke (6.5 ± 3.6), side of lesion (21R/27L), risk factors, and gross estimate of size of infarct, were comparable among the groups. Importantly, the initial motor performance measures were comparable at the start of the study, as measured days after the acute stroke.

TMS required some baseline measures of presumed cortical excitability, and required electromyography (EMG) recording, as typically occurs, from the first dorsal interosseus (FDI) muscle. These measures include resting and active motor threshold (RMT and AMT) and motor evoked potential (MEP).The technique requires optimal scalp localization for the elicitation of a MEP from the FDI in the unaffected, and, if possible, the affected limb. There are also established safety standards for the limits of stimulus intensity as a function of TMS frequency.

There were no untoward complications — particularly, there were no seizures. Electroencephalogram (EG) recordings after the treatment failed to show focal or generalized sharp activity or epileptic activity. Ten dropouts occurred because of a second stroke (4) within the follow up study, or death (2) or other non-medical complications (4). It appeared that the rTMS stimulus characteristics were safe for patients within days of an acute stroke.

The first analysis demonstrated that those treated with real rTMS were better than those treated with sham rTMS on all motor outcome scales, and the improvements persisted during the chronic phase (1–12 mos). The percent improvement in hand grip and shoulder abduction were significantly better for the rTMS treated patients compared to the sham, but the percent improvement in hip and ankle flexion were comparable. Although this is preliminary information, the presumed site of rTMS suggests that the treatment was specific for upper limb motor function.

By one year after stroke, the treated rTMS group also had better NIH stroke scale scores and modified Rankin scores than sham-treated. Improved motor outcome measures and NIH stroke scale were independent of lesion site, but there was an age effect for the NIH stroke scale change that favored the younger patients.

Whether increasing the dose of rTMS generated better scores was not apparent; in fact, the longitudinal study favored the lower frequency treatment (3Hz) at each evaluation time. There were interesting changes in cortical excitability, especially in the unaffected hemisphere of the sham-treated group.

■ **COMMENTARY**

These investigators employed the randomized controlled trial to study this group of patients with acute stroke, and they have demonstrated a positive and safe rTMS treatment effect. Much remains to be learned about the fundamental neurophysiology surrounding TMS. (The interested reader is referred to a recent review: Huerta PT, Volpe BT. Transcranial magnetic stimulation, synaptic plasticity and network oscillations. *J Neuroeng Rehabil* 2009;6:7.)

Whether impairment reduction can be optimized or hastened, and whether impairment reduction will contribute to disability reduction are questions that have stimulated controversy and research. Much of the current regimen in rehabilitation hospitals focuses reasonably, and with moderate success, on disability reduction. It is likely that the combination of bio-engineering (as with robotics and computerized electrical stimulation devices for example) and clinical neurophysiology (TMS as in this study, but, looming on the horizon, trans-cranial direct current stimulation) will continue to chip away at impairment after stroke. Whether the significant improvements, as in this well-designed study, can generate enough interest to launch a large multi-center study remains to be determined. Rehabilitation centers should be organized into research consortia and, given the low risk for many of the interventions, there should be controlled and randomized studies of new treatments and a concerted effort to generate bio-markers for recovery. When "smart" drugs are ready for common use — molecules that will improve synaptic forms of learning and translate into real world clinical outcomes — such a research infrastructure will then be poised to define rationale for best-treatment plans. ■

Anti-N-methyl-D-aspartate Receptor Encephalitis in Children and Adolescents

ABSTRACT & COMMENTARY

By Shefali Karkare, MD, and Steven Weinstein, MD

Dr. Karkare is a Fellow in the Division of Pediatric Neurology, Weill Medical College of Cornell University. Dr. Weinstein is Director of the Pediatric Comprehensive Epilepsy Program, Weill Cornell Medical School, New York Presbyterian Hospital.

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

Synopsis: *Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis has been recognized in children as young as 23 months as well as adolescents.*

Source: Florance NR, Davis RL, Lam Christopher et al. Anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents. *Ann Neurol* 2009;66:11-18.

IMMUNE MEDIATED DISORDERS OF THE NERVOUS SYSTEM are increasingly recognized as a primary cause of neurologic symptoms and injury. This list now includes antibodies to NR-1 subunits of anti-N-methyl-D-aspartate receptors (NMDAR) , initially described in association with ovarian teratomas, presenting with an early encephalitis picture that included neuropsychiatric symptoms and autonomic instability. The entity has been identified in women without neoplasm, men, and now in 32 children.

The incidence of NMDAR encephalitis is unknown but must be relatively common, with 81 patients in an eight-month period having identifiable antibodies. The group included 32 children <18 years old, eight followed at Children's Hospital of Philadelphia and the remainder from outside institutions using serum and cerebrospinal fluid (CSF) assays. The majority were female (24/32), and the frequency of ovarian teratomas was lower than the adult figure of 56%: 31% (8/26) in girls ≤18 years old ($p = 0.05$), and 9% (1/11) in girls ≤14 years old ($p = 0.008$). None of the males had a tumor.

A viral-like prodrome preceded neurologic symptoms in nearly half (48%). The majority presented with neuropsychiatric symptoms including mood, behavior or personality changes, and sleep disturbances, and progressed to severe agitation and combative or paranoid behavior. A range of severe speech problems was seen in two thirds. Early seizures were seen in six patients, though 77% had seizures later in the disease course. Movement disorders during the illness occurred in 84%, including orolinguofacial dyskinesia, choreoathetosis, and dystonic posturing. Autonomic instability in children was manifest mainly as tachycardia, hyperthermia, and hypertension, but hypoventilation and airway protection led to intubation in 23%.

CSF analysis was abnormal in 94 %, with a lymphocytic pleocytosis in 87%, occasional increased protein (13%), and oligoclonal bands found in 5/6 tested samples. All the patients had antibodies in CSF or serum that reacted with extracellular epitopes of NR1 subunit of the NMDA receptor. Twenty-one of 31 had paired CSF and serum samples, with CSF showing stronger antibody reactivity. Patients treated with plasma exchange or IVIG showed CSF positivity despite negative serum testing. The antibody titer was significantly higher in the 25% of the patients having a teratoma.

The MRI scans were abnormal in 31% (10) of the children demonstrating multifocal findings, half having only transient flair abnormalities. Seizures were observed in 77% of cases; however, the movement disorders were frequently difficult to distinguish, prompting continuous video EEG surveillance. Diffuse slowing was the most common finding during the movements.

Most of the patients were treated with immunotherapy (combination of corticosteroids, IVIG, or plasma exchange), with a few receiving rituximab and/or cyclophosphamide. Recovery began approximately six weeks after presentation, with 45% showing substantial clinical improvement, 29% having a full recovery, and 26% with limited improvement. The median time of follow-up was 4.5 months. Relapse of neurologic symptoms during tapering or completing immunotherapy occurred in 25%, and as late as one year later.

■ COMMENTARY

An immunologic disorder previously described in adults, especially those with ovarian cancers, is now recognized in children as young as 23 months. These patients appear to have viral encephalitis, but cultures and titers are normal, consistent with "idiopathic" encephalitis. The clinical findings suggest a multifocal disease but with non-specific CSF, MRI, and EEG determinations. The disorder should be considered in any child with culture- and titer-negative CSF having the onset of behavioral and sleep changes, movement disorders, seizures, and autonomic instability, including hypoventilation. Other non-infectious etiologies of encephalitis such as systemic multiorgan disorders, including lupus erythematosus, specific disorders such as Bechets, or well-recognized post-infectious disorders, should also be considered. Tumors, ovarian or otherwise, need to be excluded, but the true incidence of their future development unknown.

Recognition of this syndrome is important for diagnostic and therapeutic reasons, though questions remain as to exact mechanism of these antibodies, particularly in the absence of tumor, the role of early immunosuppression to improve outcome, or the utility of CSF antibody titers to predict relapses. ■

Value of CSF Aß/tau Profiles in Subjective and Mild Cognitive Impairment

ABSTRACT & COMMENTARY

By Michael Lin, MD

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

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

Synopsis: *Biomarkers in the cerebrospinal fluid may help in the early diagnosis of Alzheimer's disease.*

Source: Visser PJ, Verhey F, Knol DL, et al. Prevalence and prognostic value of CSF markers of Alzheimer's disease pathology in patients with subjective cognitive impairment or mild cognitive impairment in the DESCRIPA study: A prospective cohort study. *Lancet Neurol* 2009;8:619-627.

USING CURRENT CRITERIA, ALZHEIMER'S DISEASE (AD) is not diagnosed until cognitive impairment becomes severe enough to cause a functional decline in cognitive function and behavior. However, given its slowly progressive course, AD must pass through earlier stages: perhaps an asymptomatic stage, a stage of subjective cognitive impairment (SCI), and a stage of mild cognitive impairment (MCI) with objective deficits but no functional decline. Since potential disease-modifying therapies are most likely to be effective when started early, identifying which subjects in these pre-dementia states actually have AD becomes important.

In a recent *Lancet Neurology* article, Visser and colleagues suggest that cerebrospinal fluid (CSF) Aß42 and tau levels may assist with this identification. CSF Aß42 levels tend to be decreased and tau levels increased in AD subjects. The prevalence and prognostic value of this profile was therefore examined in neurologically healthy controls and subjects with SCI, nonamnestic MCI (naMCI), and amnestic MCI (aMCI). Subjects were drawn from the DESCRIPA study, a multi-center prospective study by the European Alzheimer's Disease Consortium to Develop Screening Guidelines and Criteria for Pre-dementia AD.

Out of 881 subjects enrolled at 20 centers, 168 had CSF analysis at baseline and up to three years of follow-up. An abnormal CSF Aß42/tau ratio was increasingly common in controls (28 of 89 [31%]), SCI (31 of 60 [52%]), naMCI (25 of 37 [68%]), and aMCI (56 of 71 [79%]). A normal CSF Aß42/tau profile was associated with stable or improving cognitive scores in SCI, naMCI, and aMCI. In contrast, a CSF AD profile was associated with declining cognitive scores in naMCI and aMCI. A subsequent clinical diagnosis of AD was made in none of 58 SCI subjects, eight of 34 naMCI subjects, and 27 of 70 aMCI subjects. All of the clinically diagnosed AD cases occurred in subjects with a CSF AD profile. The increase in AD risk associated with a CSF AD profile was statistically significant for aMCI (OR 26.8, 95% CI 1.6-456.4, p=0.02), but not quite for naMCI (OR 10.2, 0.55-188.10, p=0.12).

■ COMMENTARY

This was a large study involving multiple centers, with statistically significant results despite the use of different clinical scales at different centers. This suggests generalizability. On the other hand, the study needs replication outside of a memory clinic setting.

Several other caveats should be noted. A positive CSF AD profile was not specific for AD, since it was associated with eventual clinical diagnosis of a non-AD type dementia in one SCI case and one naMCI case. Longer follow-up will be of interest to determine predictive value with greater certainty, particularly in the controls and SCI cases. Serial CSF evaluations and correlation with symptom progression would also be of interest. Additionally, CSF Aß42/tau should be compared with other biomarkers, including amyloid imaging and volumetric MRI studies.

This study provides further support for recent proposals to incorporate disease biomarkers into the diagnostic criteria for AD, which should eventually permit identification at earlier stages. Future studies should consider examination of such biomarkers, including CSF Aß42 and tau measurements. ■

One Hand Clapping

ABSTRACT & COMMENTARY

By John J. Caronna, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *The hand clapping test is a quick and reli-*

able way to screen for parietal lobe neglect syndrome.

Source: Ostrow LW, Llinas RH. Eastchester Clapping Sign: A novel test of parietal neglect. *Ann Neurol* 2009;66:114-117.

IN RESPONSE TO A QUESTION, "WHAT HAPPENS IF YOU ASK patients with neglect to clap their hands?" posed by an Eastchester High School student, the authors investigated how 14 patients with acute right hemisphere strokes and hemineglect responded when asked to clap their hands. The distinct phenomenology of their responses was named the Eastchester Clapping Sign (ECS). Grading of the responses was as follows: ECS-2 = one-handed clap, respects the midline; ECS-1 = searches in the contralateral hemispace for the other hand; ECS-0 = reaches over to clap against the plegic hand.

Twelve of 14 righthanded patients had an initial ECS-2 and an acute right hemisphere stroke affecting the parietal lobe on MRI. One of the remaining two patients initially was graded ECS-1 and then worsened to ECS-2 after hemorrhagic transformation of a large right hemisphere infarct. The other patient had an ECS score that was perfusion-dependent: she fluctuated between ECS-2 and ECS-0 with changes in blood pressure. Her MRI showed a right parietal perfusion deficit without infarction.

The persistence of ECS varied. Most patients went through a progression over the first few days after stroke onset. Initially they respected the midline, then started searching for the other hand over the next 24 to 48 hours.

The authors propose the ECS as a screening test for neglect in the acute stroke setting. The sign was a consistent and unambiguous finding and easily recognizable by physicians and laypersons.

■ COMMENTARY

Patients with right hemisphere strokes are much less likely to receive rtPA due to a failure of the patients themselves and prehospital observers to recognize the presence of neglect.[1] In addition, the National Institutes of Health (NIH) stroke scale has a recognized bias toward left or dominant hemisphere strokes with language deficits. The addition of the ECS to the NIH stroke scale could increase the likelihood that patients with neglect would be recognized earlier and treated in a timely manner.

Beyond its clinical utility, the ECS should cause neurologists to meditate on the famous Zen philosophical riddle which asks, "What is the sound of one hand clapping?" Apparently, the students of Eastchester High School already have achieved a new level of enlightenment for themselves and for us.

Reference

1. Di Legge S, Fang JM, Saposnik G, et al. The impact of lesion side on acute stroke treatment. *Neurology* 2005; 65:81-86.

CME Questions

5. High levels of ß-hexachlorocyclohexane (ß-HCH) have been associated with which of the following neurological diseases?

a. Alzheimer's disease
b. Parkinson's disease
c. Both a and b
d. Neither a nor b

6. Which of the following statements is true?

a. Rituximab is a chimeric monoclonal antibody against the CD20 protein on B-lymphocytes.
b. Rituximab is beneficial for myasthenia gravis.
c. Rituximab is beneficial for polyneuropathy with IgM monoclonal gammopathy.
d. Rituximab may be beneficial for Lambert-Eaton myasthenic syndrome (LEMS).
e. All of the above

CME Objectives

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

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

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant. ■

7. rTMS has the potential to cause epileptic seizures.

a. True
b. False

8. rTMS was no better than sham treatment in the Khedr et al. clinical trial.

a. True
b. False

9. All of the following are true regarding anti-N-methyl-D-aspartate receptor (NMDAR) encephalitis in children and adolescents, *except*:

a. CSF examination is abnormal in > 90% of patients.
b. Most children are found to have teratomas.
c. Most children recover, but relapses may occur.
d. Most children present with neuropsychiatric symptoms.

10. Regarding CSF analysis in the diagnosis of Alzheimer's disease, which of the following is *false*?

a. Increased CSF Aß42 levels are associated with increased risk for Alzheimer's disease.
b. Increased CSF tau levels are associated with increased risk for Alzheimer's disease.
c. An abnormal CSF Aß42/tau profile becomes increasingly common as symptoms become more severe (controls vs. subjective impairment vs. mild cognitive impairment).
d. In the study cited, all cases eventually diagnosed clinically as Alzheimer's on follow-up had an Alzheimer's type CSF profile.
e. In the study cited, some cases with an Alzheimer's type CSF. profile were eventually diagnosed with a non-Alzheimer's type dementia.

11. All of the following are true *except:*

a. Patients with right rather than left hemisphere infarcts are less likely to receive rtPA.
b. The ECS is useful only in acute stroke.
c. The ECS distinguishes between ischemic and hemorrhagic stroke.
d. The ECS may fluctuate with progression of infarction.
e. The ECS is suitable for use by laypersons as well as physicians.

Answers: 5. b, 6. e, 7. a, 8. b, 9. b, 10. a, 11. c

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The short-term risks of bariatric surgery

Source: The Longitudinal Assessment of Bariatric Surgery (LABS) Consortium; et al. *N Engl J Med* 2009;361:445-454.

Long-term benefits from bariatric surgery have been definitely established. Nonetheless, perioperative risks associated with bariatric surgery are not insignificant, especially since persons undergoing bariatric surgery often suffer comorbidities of diabetes, hypertension, and dyslipidemia.

The LABS Consortium performed an observational study of short-term outcomes subsequent to bariatric surgery in the United States. From 2005 to 2007, data supplied by 10 different clinical sites (combined total n = 4776 first-time bariatric surgical procedures) provided information on the composite endpoint of 30-day major adverse outcomes (death, DVT, postoperative intervention, and extended hospital stay). Roux-en-Y bypass was performed on approximately 70% of subjects; the majority of the other patients underwent gastric banding.

Death occurred in 0.3% of subjects within 30 days; an additional 4% of subjects experienced at least one adverse event included in the composite primary endpoint. A previous history of DVT was associated with greater likelihood to incur a postoperative adverse event; additionally, the higher the BMI (mean BMI in this report = 46.5 kg/m^2), the greater the frequency of adverse events.

Bariatric surgery has significant associated risks. For most appropriately selected patients, the long-term benefits far outweigh these risks, but patients need to be informed of the potential for serious adverse outcomes. ■

Parsing the death toll of COPD

Source: Zvezdin B, et al. *Chest* 2009; 136:376-380.

Worldwide, COPD is the fourth leading cause of death; unless current trends reverse, the toll will rise. Mortality rates associated with hospitalized acute exacerbations of COPD have been as high as 30%; the mortality in the 1 year after hospitalization is as high as 43%. Some of this mortality is directly attributable to COPD; however, other prominent comorbidities (e.g., CVD, pulmonary embolism) are also responsible. Often, because post-mortem examination is limited, the cause of death can only be opined. To provide greater clarity, Zvezdin et al report on autopsies of 43 patients who died within 24 hours of COPD hospital admission.

The mean age of the study subjects was 70. According to autopsy results, more than half of the deaths were attributed to diagnoses other than COPD: heart failure (in 37%) and pulmonary embolism (in 21%). The authors also separate pneumonia as a "non-COPD" cause of death (occurring in 28%), defining COPD death as those individuals who die of respiratory failure due to COPD progression (14%).

If these results (from a Serbian tertiary care university hospital specializing in pulmonary diseases) are generalizable to U.S. populations, clinicians will need to exercise greater vigilance, enhanced preventive techniques, and intensified intervention for potentially fatal comorbidities when patients are admitted for acute COPD exacerbation. ■

Vardenafil and premature ejaculation

Source: Aversa A, et al. *Int J Impot Res* 2009;21:221-227.

Although clinicians are much more familiar with erectile dysfunction, over the lifespan premature ejaculation (PEJ) is more common. A much smaller percentage of men with PEJ seek help, attributable to factors such as embarrassment, absence of available FDA-approved medications, and lack of public awareness of PEJ as an important sexual health dysfunction.

The technical definition of PEJ is a matter of controversy, although most experts agree that consistent unintended/unwanted ejaculation within 1 min that causes distress is satisfactory for the diagnosis.

The most commonly used metric for measuring PEJ is intravaginal ejaculatory latency time (IELT), or the time after vaginal intromission at which ejaculation occurs. Population studies have suggested that in established heterosexual couples, typical IELT is 6-10 min. Subjects enrolling in PEJ trials typically have an IELT of 30-90 sec, or even ejaculation ante portis (prior to intromission). The above definition would, by construction, seem to exclude gay men or ejaculation involving other orifices/body parts, but the similarities of diagnosis and management of PEJ in gay couples suggest that IELT, while at times anatomically inconsistent, incorporates the broader concepts

of early ejaculation in a variety of sexual settings.

SSRIs have an established role in management of PEJ. Success with SSRIs is greatest when taken on a maintenance schedule; however, patients would generally prefer as-needed administration, all things being equal.

Aversa et al studied men with PEJ (n = 42), all of whom consistently experienced IELT < 1 min. Patients were randomized (double-blind) to placebo or vardenafil 10 mg administered 15-30 min before sexual activity. The primary outcome was change in IELT.

Use of vardenafil provided a significant improvement in IELT (from 36 sec to 4.5 min) compared with placebo (IELT went from 42 sec to 54 sec). The tolerability of vardenafil is well established. Vardenafil appears to be a viable option for PRN treatment of PEJ. ■

Testosterone, depression, and hypogonadal men

Source: Shores MM, et al. *J Clin Psychiatry* 2009;70:1009-1016.

SUBTHRESHOLD DEPRESSION (sDEP), also known as minor depression, occurs in as many as 1 of 4 elderly patients. Although by definition the symptom burden of sDEP is less than major depressive disorder (MDD), it is more common than MDD and is still associated with diverse negative outcomes including decreased quality of life and function, and increased morbidity, mortality, and health care utilization.

Symptoms of hypogonadism include fatigue, decreased libido, and dysphoria, any of which may also be manifestations of depression. Shores et al studied the impact of testosterone replacement in hypogonadal men (total testosterone < 280 ng/dL) meeting DSM-IV criteria for sDEP.

This double-blind trial randomized adult men (n = 33) to testosterone gel 7.5 g/d or placebo for 12 weeks. The primary outcome was change in the HAM-D depression score.

At the end of the trial, testosterone-treated men had a significantly improved HAM-D score compared to placebo, and the percent with remitted sDEP was dramatically different (52.9% vs 18%) favoring testosterone.

No serious testosterone-attributable adverse effects were seen. Testosterone replacement shows benefit for improving sDEP in hypogonadal men. ■

Aspirin after colon cancer diagnosis

Source: Chan AT, et al. *JAMA* 2009; 302:649-658.

MOST COLORECTAL CANCERS OVEREXPRESS cyclo-oxygenase 2 (COX-2). Primary prevention with aspirin (ASA) is associated with reduced risk for colon cancer and colonic adenoma. Secondary prevention with ASA (and celecoxib) is effective in reducing risk of new adenomas in persons who have been previously diagnosed with colonic neoplasia. Because ASA has recognized toxicities, including cerebral hemorrhage and GI bleeding, it is important to determine whether use of ASA in high-risk subjects (persons previously diagnosed with colon cancer) provides net benefit for overall and/or colon cancer-specific mortality.

The Physicians' Health Study and the Nurses' Health Study are observational studies, providing a window of observation for the role of ASA in both primary and secondary prevention. A cohort within both populations took maintenance ASA prior to any diagnosis of colon cancer, and further information about effects of ASA in persons who developed colon cancer and continued with ASA subsequent to the cancer diagnosis (vs subjects who did not take ASA after a diagnosis of colon cancer) is presented here.

Of subjects who developed colon cancer (n = 1279) in these two study populations (combined), there were statistically significant differences in total mortality (35% vs 39%) and colon cancer-related mortality (15% vs 19%) favoring use of ASA. Concordant with current thinking on the putative mechanism of ASA benefit, the risk reduction was greatest in persons whose colon cancer overexpressed COX-2. Despite these favorable results, the authors caution that routine utilization of ASA post colon cancer might be considered premature since these data are observational; placebo-controlled randomized trials are needed for confirmation. ■

The Emperor's new vertebroplasty?

Source: Buchbinder R, et al. *N Engl J Med* 2009;361:557-568.

VERTEBROPLASTY (VERT) HAS RECENTLY enjoyed increased popularity as treatment for painful osteoporotic vertebral fractures. Observational or open-label studies have provided most of the supportive information. Enthusiasm for other previously popular surgical procedures has been dampened when double-blind randomized trials have failed to confirm positive outcomes: Two randomized trials in the last 7 years comparing arthroscopy for knee osteoarthritis found no outcomes difference when compared to placebo.

Buchbinder et al performed a randomized, double-blind, sham procedure-controlled trial of VERT for painful osteoporotic fracture in 78 participants. The primary outcome was pain reduction, which did not differ at weeks 1, 3, or 24 after treatment between intervention and sham intervention.

The Buchbinder study was published immediately preceding another VERT trial in the *New England Journal of Medicine* examining pain and disability at 1 month post intervention, which similarly did not find positive outcomes. These trials call for closer evaluation of the (potential) value of VERT. ■

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WHO Issues Global Alert on Antiviral Use

In this issue: WHO recommendations for antiviral use for H1N1 flu; antibiotic use trends for acute respiratory tract infection; denosumab clears FDA Expert Panel; FDA Actions.

Antiviral Recommendations for H1N1

The World Health Organization (WHO) has issued a global alert and response regarding the use of antivirals for pandemic H1N1 flu, reiterating that antivirals should be used to prevent severe illness and death in children and adults. The neuraminidase inhibitor oseltamivir (Tamiflu®) is recommended for patients who initially present with severe illness or whose condition begins to deteriorate. H1N1 remains sensitive to the neuraminidase inhibitors such as oseltamivir despite isolated reports of resistance earlier this year. The WHO recommends that clinicians in communities where the virus is circulating widely assume that patients with flu-like symptoms have H1N1 and not wait for laboratory confirmation. Most patients with pandemic flu experience typical flu symptoms and recover within a week. These patients do not need antivirals. But in patients with severe illness, studies have shown that early treatment, within the first 48 hours, is associated with better clinical outcomes. WHO also states that if oseltamivir is unavailable zanamivir (Relenza®) may be used in its place. This recommendation applies to all patient groups including children and pregnant women. The WHO statement comes in response to an article in the *British Medical Journal* suggesting neuraminidase inhibitors provide minimal benefit for children with seasonal influenza and have little effect on asthmatic exacerbations or use of antibiotics (Shun-Shin M, et al. *BMJ* 2009;339:b3172). ■

Antibiotic Use Declines Overall, While Use of Broad-Spectrum Increases

Physicians are prescribing fewer antibiotics for acute respiratory tract infections (ARTIs), but if an antibiotic is used, it is more likely to be a broad-spectrum drug. Using data from 1995 to 2006, antibiotic trends were reviewed from a national database for ARTIs, which included otitis media (OM). Children younger than age 5 were seen less frequently for ARTI than in the past, and they were less likely to be prescribed an antibiotic (36% reduction; 95% confidence interval [CI], 26%-45%). Among children age 5 or older, ARTI visit rates remained stable but antibiotic prescription rates decreased by 18% (95% CI, 6%-29%). Excluding otitis media, antibiotic prescription rates decreased by 41% among all age groups. Prescription rates for a penicillin, cephalosporins, and sulfonamide/tetracycline decreased while the rate of prescriptions for azithromycin increased, making it the most commonly prescribed macrolide for ARTI and OM. Among adults, quinolone prescriptions also increased. The authors conclude that overall antibiotic prescription rates for ARTI decreased in the last 10 years; however, prescription rates for

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broad-spectrum antibiotics increased significantly (Grijalva CG, et al. *JAMA* 2009;302:758-766). This study points out the success of multiple campaigns to decrease antibiotic use for ARTIs, which are primarily caused by viruses. However the increasing use of broad-spectrum antibiotics is concerning. ■

Denosumab Receives Conditional Approval from FDA Expert Panel

Denosumab is a new human monoclonal antibody that suppresses osteoclast function and thus inhibits bone resorption. It is being evaluated by the FDA for treatment of osteoporosis in men and women, and although it has not yet been approved, a recent FDA Expert Panel has given conditional approval paving the way for full FDA approval this fall. Two recently published, industry-sponsored studies suggest the drug is effective in 2 different populations. In the first study, more than 1400 men receiving androgen-deprivation therapy for nonmetastatic prostate cancer were randomly assigned to receive denosumab 60 mg SQ every 6 months or placebo for 2 years. The primary endpoint was change in bone mineral density (BMD) at the lumbar spine, with secondary endpoints of change in BMD in the hip as well as fracture incidence. At 24 months, BMD increased in the lumbar spine with denosumab (5.6% increase vs 1% decrease for placebo; $P < 0.001$). BMD was also increased in the total hip, femoral neck, and distal radius, and the effect was maintained for 36 months. New fracture rate was also decreased with treatment (1.5% vs 3.9% with placebo; $P = 0.006$). Rates of adverse events were similar in both groups (Smith MR, et al. *N Engl J Med* 2009;361:745-755).

In the second study, 7868 postmenopausal women with low BMD were randomized to denosumab 60 mg SQ every 6 months or placebo for 36 months. The primary endpoint was new vertebral fractures. Denosumab was associated with a reduction in vertebral fractures (2.3% vs 7.2% placebo; $P < 0.001$), a reduction in hip fractures (0.7% vs 1.2% placebo; $P = 0.04$), and a smaller reduction in nonvertebral fractures. There was no increase in risk of cancer, infection, cardiovascular disease, delayed fracture healing, hypocalcemia, or osteonecrosis of the jaw in this study (Cummings SR, et al. *N Engl J Med* 2009; 361:756-765).

These last findings are important because the FDA's Expert Panel expressed concerns about infection and cancer data in giving a recommendation to approve denosumab when the FDA votes on the drug in October. If approved, which seem likely, denosumab will be marketed by Amgen under the trade name Prolia™. ■

FDA Actions

The FDA is requiring new boxed warnings on TNF-blockers regarding the risk of lymphoma and other malignancies in children and adolescents who have received the drugs. The new labeling will include warnings regarding cases of leukemia in adults, adolescents, and children, as well as new onset psoriasis. The labeling will also include a revised Medication Guide to reflect the safety information. Products subject to the new boxed warning are infliximab (Remicade®), etanercept (Enbrel®), adalimumab (Humira®), and the recently approved agents certolizumab pegol (Cimzia®) and golimumab (Simponi™). These TNF-blockers are used to treat rheumatoid arthritis, juvenile idiopathic arthritis, psoriatic arthritis, plaque psoriasis, Crohn's disease, and ankylosing spondylitis. The warning is based on reports of nearly 50 cases of various cancers associated with the drugs, of which half were lymphomas.

The FDA has approved a new dipeptidyl peptidase-4 (DPP-4) inhibitor for the treatment of type 2 diabetes. Bristol-Myers Squibb and AstraZeneca's saxagliptin (Onglyza™) is the second DPP inhibitor approved after sitagliptin (Januvia®). It is the first drug approved since the FDA changed its standards for diabetes drug approvals, requiring evidence of cardiovascular safety. While saxigliptin has not shown evidence of higher rates of cardiovascular disease, the FDA is requiring post-marketing studies to specifically look at cardiovascular safety in high-risk populations. Saxigliptin is dosed once daily and is approved as monotherapy or in combination with metformin, sulfonylureas, or thiazolidinediones.

The FDA has announced that it is reviewing adverse event reports of liver injury in patients taking the weight-loss drug orlistat, marketed as the prescription drug Xenical® and over the counter as Alli®. The agency has received 32 reports of serious liver injury in patients taking the drug in the last 10 years. Of these, 6 resulted in liver failure. Almost all of the reports are from outside the United States. The FDA is not recommending patients discontinue the drug, but is suggesting that those who have used orlistat should consult a health care professional if they develop jaundice, fever, fatigue, brown urine, or other symptoms of liver injury. ■