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INSIDE

Financial Disclosure: *Neurology Alert's* editor in chief, Matthew Fink, MD, is a retained consultant for MAQUET. Peer reviewer M. Flint Beal, MD; executive editor Leslie Coplin; and managing editor Neill Kimball report no financial relationships relevant to this field of study.

Solvents and the Risk of Parkinson's Disease

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

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Dr. Nirenberg reports no financial relationships relevant to htis field of study.

Synopsis: *Exposure to specific solvents, and trichloroethylene in particular, is associated with an increased risk of Parkinson's disease.*

Source: Goldman SM, et al. Solvent exposure and Parkinson disease risk in twins. *Ann Neurol* 2011;DOI:10.1002/ana.22629.

PARKINSON'S DISEASE (PD) HAS BEEN CLOSELY LINKED TO BOTH GENETIC AND environmental factors. In prior studies, environmental exposures associated with PD have included pesticides, well water consumption, and residency in rural areas; inverse risk factors have included smoking and coffee use. Some studies have implicated solvents in PD risk, but data have been lacking about whether (and which) solvents may be involved.

In this study, the authors examined the potential association between PD and exposure to six specific solvents. They used a case-control study design, with 99 pairs of twins who were discordant for PD status. Study subjects, all of whom were male, were recruited from the National Academy of Sciences/National Research Council World War II Veteran Twins Cohort. Structured questionnaires were used to obtain detailed lifetime occupational and hobby histories from each subject. Expert raters, blinded to PD status, then used this information to infer each subject's lifetime exposure to these six solvents.

The authors found that ever exposure to trichloroethylene (TCE) was associated with an increased risk of PD (odds ratio [OR], 6.1; $P = 0.034$). There also were non-significant trends toward increased PD risk with

ever exposure to perchloroethylene (PERC; OR, 10.5; P = 0.053) or carbon tetrachloride (CCl_4; OR, 2.3; P = 0.088). There were similar findings when they examined the duration of exposure and cumulative lifetime exposure to these solvents. Based on these findings, the authors conclude that solvents, and TCE in specific, are associated with an increased risk of PD.

■ COMMENTARY

In this small but well-designed epidemiological study, the authors provide new evidence to support the association between solvent exposure and PD, with a significant association between PD and TCE, and similar trends for PERC and CCl_4. Given that these solvents are commonly used in industry, dry cleaning, and household products, the findings have major public safety implications.

Study strengths include the population-based study design and use of twin pairs to minimize potential confounders. Limitations include the small sample size, retrospective study design, and inferred calculation of solvent exposure. In addition, the study sample consisted exclusively of male World War II veterans, such that the results may not be generalizable to other populations.

In summary, this study suggests that exposure to specific solvents may increase the risk of PD. Given the major public health implications of these findings, further studies in larger, prospective cohorts are warranted. ■

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media, a division of Thompson Media Group, LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 105109, Atlanta, GA 30348.

Subscriber Information

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1 year with free AMA Category 1 credits: $319
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Another Major Syndrome of the Minor Hemisphere — Othello Syndrome

ABSTRACT & COMMENTARY

By John J. Caronna, MD

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

Synopsis: *Neurological disease affecting the non-dominant frontal lobe has been associated with a syndrome of "delusional jealousy," referred to as Othello syndrome.*

Source: Graff-Radford, J, et al. Clinical and imaging features of Othello's syndrome. *Eur J Neurol* 2012;19:38-46.

THE LEFT HEMISPHERE HAS BEEN TERMED THE "MAJOR OR dominant" hemisphere because of its linguistic and lexical abilities. The term "minor," however, does not do justice to the right hemisphere's role in attention, in the integration of polymodal sensory information, and in emotional processes. Damage to the right hemisphere can impair the affective aspects of communication that are manifested by dysprosody, inability to abstract, loss of understanding of the figurative aspects of language, and lack of comprehension of facial expressions. Other "syndromes of the right hemisphere" include unilateral spatial neglect, topographical disorientation, anosognosia, misidentification syndromes, and neuropsychiatric disorders.[1]

The delusion of infidelity of a spouse or lover, also called delusional jealousy, has been termed Othello syndrome (OS) after the character in Shakespeare's play. OS has been associated with psychiatric conditions, but occurs more commonly in neurological disorders including stroke, brain trauma, brain tumor, neurodegenerative disease, normal pressure hydrocephalus, endocrinopathy, and dopaminergic drug use.[2]

In the present study, a retrospective case review, the authors sought to document the clinical and MRI features of OS. One hundred and five patients with delusional jealousy were identified in the medical records of the Mayo Clinic. The average age at onset was 68 years (range 25-94), and 62% of the patients were men. OS was associated with a neurologic disorder in 73 (69.5%) and with a psychiatric condition in 32 (30.5%).

Of the 73 patients with a neurologic disorder, 56 (77%) had a neurodegenerative disorder: 20 had diffuse Lewy

Body disease, six had Parkinson's disease (PD), and three had PD with dementia. Six patients with PD without dementia developed OS after starting or increasing the dose of dopamine agonists. One other patient developed drug-induced OS after increasing the dose of valproic acid. Symptoms of OS resolved after decreasing the dose. Eight patients with OS had structural lesions (meningioma, stroke, encephalomalacia, subdural or cerebral hemorrhage), and seven of them had right frontal pathology.

The authors conclude that OS occurs more frequently in neurologic than in psychiatric disorders, and this delusion is associated with dysfunction of the frontal lobes, especially the right frontal lobe.

■ COMMENTARY

A delusion is a fixed, idiosyncratic belief that is held to, despite evidence or arguments brought against it. Delusions usually are taken to indicate mental illness; for example, the delusions of grandeur or persecution in schizophrenics and the delusions of unworthiness in depressed patients.

In contrast, Othello Syndrome, like the Capgras and Fregoli misidentification syndromes, is due to organic causes: dopaminergic hyperactivity or defective information processing due to a brain lesion in the right hemisphere. Unlike the aphasic syndromes of the left hemisphere and the misidentification syndromes of the right, both of which have been explained in terms of "disconnection syndromes," the Othello Syndrome has yet to be interpreted in terms of a neuroanatomical map. Therefore, although the syndrome has been associated with lesions of the right frontal lobe, the association remains more phrenological than physiological. The right hemisphere specific syndromes remain an area of active neuroscience research.

By now, most readers will have come to the conclusion that Othello, in fact, did not have his eponymous syndrome. Othello was deceived rather than deluded about Desdemona's alleged infidelity. Therefore, those who prefer to use the term "delusional jealousy" rather than "Othello syndrome" are encouraged to do so. ■

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Cortical Lesions are an Important Component of Multiple Sclerosis

ABSTRACT & COMMENTARY

By Timothy Vartanian, MD, PhD.

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Dr. Vartanian reports that he is on the speakers bureau for UCB Pharma and Cyberonics..

Synopsis: *In a carefully studied group of patients who underwent brain biopsies for atypical presentations of multiple sclerosis, cortical demyelination or cortical inflammatory lesions were demonstrated in about half.*

Source: Lucchinetti CF, et. al. Inflammatory cortical demyelination in early multiple sclerosis. *N Engl J Med* 2011;365:2188-2197.

CORTICAL LESIONS IN MULTIPLE SCLEROSIS (MS) HAVE BEEN largely overlooked until recently for two major reasons: 1) histology protocols for myelin stains generally require de-staining the tissue until the cortex is unstained, and 2) conventional MRI protocols are surprisingly insensitive in detecting cortical lesions.[1] Initial efforts to define the cellular composition of cortical lesions in multiple sclerosis (MS) enigmatically revealed a paucity of inflammatory cells in these lesions.[2-4] This presented a dichotomy: white matter lesions contained perivenular lymphocytes and abundant tissue macrophages, whereas grey matter lesions showed little in adaptive and innate immune response. An ensuing hypothesis suggested cortical demyelination occurred independent of cellular immunity. Lucchinetti et al's report challenges this concept of "bland" demyelination in cortex by showing that a significant percentage of cortical lesions contain inflammatory infiltrates characteristic of white matter lesions.[5]

Biopsies were performed at the time of clinical presentation for patients in whom neoplasms or other neurologic disease were considered. Typically, the target lesion was in the white matter, and cortex was collected en route. Within this larger cohort of biopsied patients, sufficient cortex for histologic examination was available in 138 patients. Of those patients, 53 (38%) showed evidence of cortical demyelination, 12 (9%) showed cortical inflammation without demyelination, and 73 (53%) showed normal cortex. More than half (56%) of the 138 patients studied had comprehensive clinical follow up (median time to follow-up: 3.5 years); of these 77 patients, three-fourths were found

to fulfill criteria for clinically definite MS and 25% for a clinically isolated syndrome. Since biopsies were performed early after clinical presentation, it follows that cortical lesions occur early in the course of MS.

In a sub-analysis of 41 patients with cortical demyelination, 27 (66%) showed the presence of foamy macrophages in cortical lesions consistent with active demyelination. Activated microglia were identified in all demyelinating lesions studied in this sub-analysis. Sufficient tissue was available for an analysis of lymphocytic infiltrates in 38 patients. Perivascular CD3+ and CD8+ T-cells were present in 82% and 77% of lesions respectively. Furthermore, patients with cortical lesions were more likely to have overlying meningeal inflammation. Taken together, these data support the concept that inflammatory demyelination is relatively common in early cortical lesions.

This study provides evidence supporting three important concepts in MS: 1) that cortical lesions occur early in the clinical course of MS; 2) that early cortical lesions contain a repertoire of inflammatory cells identified in established active white matter lesions; and 3) that resolution of inflammation in cortical lesions is more rapid.

■ COMMENTARY

It seems most likely that the pathophysiologic mechanisms leading to demyelination in cortical and white matter lesions of MS share a common initial pathway. If so, then why is the cellular phenotype of cortical lesions so different from that of white matter lesions? A clue comes from examination of the leukocortical lesions — those lesions that span white matter and grey matter from a single center of origin. Established leukocortical lesions show consistent demyelination in both the white and grey matter portions of the lesion. However, these established leukocortical lesions display abundant activated innate immune cells in the white but not the grey matter portions of the lesions.

Thus, reconciling Luccinetti's serendipitous findings with those of studies that find a paucity of inflammatory cells in cortical lesions may be a simple matter related to time of sampling in the lesion's evolution. The cellular context in which demyelination occurs may dictate the rapidity of the inflammatory response's resolution. It is well known that neurons, and particularly grey matter, suppress inflammation when compared to white matter or non-neuronal tissues. Thus, inflammatory demyelination in the cortex may resolve rapidly, whereas inflammatory demyelination in the white matter may be prolonged.

Criticism of Luccinetti's approach has been repeatedly made: MS that requires biopsy for diagnosis is atypical, thus the pathological findings do not apply to typical MS. Although this criticism holds some validity, it should be remembered that the spectrum of clinical presentations for MS is broad. What we learn from one edge of the spectrum undoubtedly bears relevance to the entire disease. Biopsies, along with the rare mortalities that occur early after onset of symptoms, provide glimpses into the histopathologic features of the early lesion.[5,6] In this study, while atypical lesions were the biopsy target, the tissue under study here was obtained en passant. As a consequence, this study cannot be meaningfully criticized for analysis of atypical lesions. Since cortical lesions were not identified by MRI and were not the biopsy target, there is some randomness in the cortex sampled thus making the findings even more impressive. The insights gained from this innovative work are numerous and open important new avenues of investigation. This novel approach has yielded heretofore-unrecognized findings that further our understanding of MS pathophysiology. ■

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Muscle Complications Due to Statins

ABSTRACT & COMMENTARY

By Michael Rubin, MD

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

Synopsis: *A small percentage of patients taking statins may develop muscle symptoms (pain and weakness) but elevated CK is rare.*

Source: El-Salem, K, et al. Prevalence and risk factors of muscle complications secondary to statins. *Muscle Nerve* 2011;44;877-881.

WHICH RISK FACTORS PREDISPOSE PATIENTS TO MUSCLE complications from statin therapy? At King Abdullah University Hospital (KAUH), Irbid, Jordan, 345 consecutive patients receiving statins were enrolled during a 12-month period into a prospective comparative study. Subjects were compared to 85 age- and sex-matched controls to determine the prevalence and risk factors of statin-associated muscle complications. Neurological symptoms predating statin therapy were analyzed carefully to distinguish them from those beginning after statin administration. Controls were recruited from the general medicine and neurology clinics of KAUH, were not on statins, and were usually seen for headaches. Statistical analysis encompassed Chi-square and independent-sample t-tests, included calculation of crude odds ratios and their 95% confidence intervals, with $P < 0.05$ considered statistically significant.

Among 345 statin-treated patients (207 men and 138 women; mean age of 57 years), muscle symptoms were reported in 21%, compared to 5.9% of controls, and included muscle pain, tenderness, fatigue, weakness, stiffness, or cramps ($P = 0.0013$). Statins used included atorvastatin (n = 219), simvastatin (n = 58), fluvastatin (n = 47), pravastatin (n = 19), and rosuvastatin (n = 7). Weakness, always mild (4+ on MRC scale), usually bilateral in both arms and legs, and proximal more than distal, was found on examination in 15% of those who reported muscle symptoms, approximately 3.2% of the total group, but was not found in any patient who denied muscle symptoms, nor in any control. Elevated creatine kinase (CK), three to fourfold normal, was seen in only two patients, both of whom had both muscle symptoms and weakness, and both of whom also were taking fibrates. Elevated CK was not seen in any patient with symptoms alone, without clinical weakness. Age over 60 years, greater than 10-month statin usage, a history of diabetes or stroke, and lower body mass index all were associated with a statistically significant increased risk of developing muscle-related symptoms. Statin dose, gender, thyroid, liver, kidney, and cardiovascular disease did not correlate with symptom development. Specific patient and disease characteristics appear to associate with adverse reactions to statins.

■ COMMENTARY

Although the precise mechanism of statin-induced myopathy remains uncertain, multiple mechanisms have been proposed. Depletion of isoprenoids, the lipid byproducts of the HMG-CoA reductase pathway, may reduce protein prenylation, which negatively affects small GTPases and lamins, causing vacuolization of muscle fibers, organelle swelling and degeneration, and apoptosis. Statins may inhibit ubiquinone or coenzyme Q10 synthesis, which would interfere with mitochondrial respiratory chain function and energy production. Impaired calcium metabolism may open ryanodine receptors resulting in greatly increased intracellular calcium. Autoimmune pathways are implicated as statins activate T lymphocytes and appear to upregulate MHC-1 expression. Sarcolemmal cholesterol reduction may destabilize the membrane by altering membrane fluidity and integrity.[1] Mice studies suggest that protection from statin complications may be obtained by an exercise program prior to statin initiation.[2] What can be done once statin myopathy is evident? Options include switching to another statin at a lower dose, using longer acting statins (including rosuvastatin and atorvastatin), and switching to non-statin lipid-lowering agents. ■

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CLIPPERS: Is it for Real?

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

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

Synopsis: *CLIPPERS is a recently described steroid-responsive neurological syndrome manifested by subacute progressive cerebellar and brainstem inflammation with characteristic MRI appearance.*

Sources: Simon NG, et al. Expanding the clinical, radiological and neuropathological phenotype of chronic lymphocytic inflammation with pontine perivascular enhancement responsive to steroids (CLIPPERS). *J Neurol Neurosurg Psychiatry* 2012 83:15-22. Kira J. The expanding phenotype of CLIPPERS: Is it a disease or a syndrome? *J Neurol Neurosurg Psychiatry* 2012 83:2-3.

CHRONIC LYMPHOCYTIC INFLAMMATION WITH PONTINE PERIvascular enhancement responsive to steroids, known by the acronym CLIPPERS, is a recently described neurological entity manifested by steroid-responsive cerebellar dysfunction. The etiology of the entity is unknown and may be an independent clinical entity (a disease) or a syndrome caused by an underlying medical disorder. The authors of this paper add five new cases to the literature, all

of which include neuropathology.

All five cases manifested gait ataxia. In three cases, this was the presenting symptom. In one case, headaches and fatigue were the presenting symptoms and in another, right facial nerve palsy was the presenting symptom. Most patients developed dysarthria and limb ataxia, and four of five patients developed cognitive dysfunction. The mean age of onset was 43 (range 20-65), affecting four men and one woman. All patients had characteristic MRI features including numerous punctate or nodular gadolinium enhancing lesions bilaterally in the pons, cerebellum, and/or brachium pontis without mass effect, and with minimal or no vasogenic edema and no restricted diffusion on diffusion-weighted MRI. Patients with cognitive impairment also demonstrated cerebral atrophy. Cerebrospinal fluid (CSF) had mild lymphocytic pleocytosis and/or elevated protein in some cases. Two patients had parotid gland uptake on body PET scan; parotid biopsies were either normal or demonstrated nonspecific inflammation. One patient's CSF demonstrated oligoclonal banding. Two patients had positive ANA, one with positive SS-A.

All five patients eventually underwent brain biopsy and all cases demonstrated a predominantly white matter-based perivascular and parenchymal lymphohistiocytic inflammatory infiltrate with accompanying reactive gliosis. There were no neutrophils or eosinophils in any of the specimens. The perivascular inflammation centered around both small arteries and veins. All cases demonstrated axonal injury, and some elements of demyelination (not focal) were seen in three cases. There was no evidence of vasculitis. The majority of white blood cells were CD4+ lymphocytes and monocytes. There was no evidence of atypical lymphocytosis, EB virus infection, or viral inclusions.

All patients demonstrated a marked improvement with corticosteroid therapy, although it was often incomplete and relapse was common upon withdrawal of the steroids. In follow-up imaging, all patients had resolution of the gadolinium enhancing lesions, but they all developed cerebellar atrophy and three of five developed cortical atrophy. Clinical relapses were associated with recurrence of the gadolinium enhancement.

■ COMMENTARY

In neurology there are a number of poorly understood clinical entities that respond to steroids. The most famous one is variably known as Hashimoto encephalopathy or SREAT (steroid-responsive encephalopathy with associated anti-thyroid antibodies). Experts debate whether this syndrome is a disease in its own right. For the time being, CLIPPERS can be added to that list as well. That said, one feature that distinguishes CLIPPERS from SREAT is the typical MRI appearance, which does suggest that there may be some underlying disease. The difficulty in diagnosis is that there are other neurological disorders, notably neuro-Behcet disease which can manifest without systemic symptoms and can cause a relapsing posterior fossa lymphocytic inflammatory disorder. It is not yet clear that CLIPPERS is merely describing cases of Behcet disease isolated to the CNS. Since there is no diagnostic biomarker for CLIPPERS, neurologists who encounter cases of suspected CLIPPERS, should make sure to investigate for all other potential causes, including Behcet, sarcoidosis, lymphoma, and systemic connective tissue diseases, to name a few. It is important to note that patients do respond to intravenous corticosteroids, and a steroid trial should be administered, once lymphoma has been excluded. ■

Posterior Reversible Encephalopathy Syndrome, Seizures, and the EEG

ABSTRACT & COMMENTARY

By Steven Karceski, MD

Director of Clinical Trials, Cornell Comprehensive Epilepsy Center, Weill Cornell Medical College

Dr. Karceski reports he is on the speakers bureau for GlaxoSmithKline, Cyberonics, and Pfizer; and receives research support form Novartis and Cyberonics.

Synopsis: *This clinical study evaluated patients with posterior reversible encephalopathy syndrome to determine the kind of seizures they experienced, abnormalities on EEG, and to correlate this with findings on neuroimaging (MRI).*

Source: Kastrup O, et al. Posterior reversible encephalopathy syndrome (PRES): Electroencephalographic findings and seizure patterns. *J Neurol* 2011 DOI 10.1007/s00415-011-6362-9.

POSTERIOR REVERSIBLE ENCEPHALOPATHY SYNDROME (PRES) is a clinical and radiological diagnosis characterized by changes in mental status, headaches, visual obscurations, and seizures. Radiographically, there are characteristic changes on MRI, consisting of both white and gray matter hyperintensities. As the name of the syndrome suggests, MRI changes usually occur in the posterior quadrants of the brain and are usually symmetric. PRES is most often associated with hypertension (usually quite high), eclampsia, neurotoxins (such as chemotherapeutics), and immu-

nosuppressants. The connection between these causes and the radiologic findings is unclear, though one hypothesis is that there is vasogenic leakage through the blood-brain barrier, accounting for the clinical and imaging findings.

In the medical literature, there is scant information about PRES and associated EEG findings. Kastrup and colleagues carefully reviewed the EEGs in 49 adults (ages 18-66) who were treated for PRES at the University of Duisburg-Essen, between 2004 and 2011. They performed a retrospective chart review of 49 patients who had radiologically confirmed PRES and 38 of these patients also had seizures. Of the 38 who had seizures, 17 had one or more EEGs during the course of their illness. Of the 17, one (5%) had focal visual seizures, and one (5%) had focal motor seizures. Two (12%) had serial grand mal seizures, defined as seizures that recurred within the first hour of the initial seizure. Three (17.6%) had recurrent grand mal seizures, defined as seizures that recurred within the first 3 hours of the initial seizure. None of the patients had status epilepticus nor seizures for more than 1 day after the initial seizure. About one-half (53%) were treated for their seizures.

EEGs were abnormal in all 17 patients. Diffuse slowing to the theta range was the most common finding, occurring in 13 of the 17 patients (76.5%). Diffuse delta was the next most common finding in 23.5%. Epileptiform discharges occurred in one patient, consisting of occipital sharp-slow wave discharges. One patient had periodic lateralized epileptiform discharges in the left hemisphere.

Kastrup et al noted that a single "grand mal" seizure was the most common type of seizure to occur in PRES. Serial or recurrent grand mal seizures occurred less often. Though described in the medical literature, status epilepticus and chronic epilepsy did not occur in this case series. No correlation was found between the occurrence of seizures and the pattern of abnormalities on MRI. The most common finding on EEG was diffuse slowing (theta and delta); infrequently, epileptiform discharges were recorded.

■ COMMENTARY

PRES is known to cause seizures. This makes sense given the cortical involvement in most people who develop this syndrome. In the medical literature, most descriptions of the seizures that occur in PRES come from case series or case reports. Convulsions, focal seizures, and status epilepticus all have been reported. In most people, the seizures are self-limited, acute, and usually do not become chronic epilepsy.

Although very helpful, Kastrup's study is limited. Of the 49 patients, EEG results were available in only one-third (34%). Of the 38 who had seizures, an EEG was performed in fewer than one-half (44%). This is a limitation of a retrospective chart review; not all patients will have undergone the testing that the authors were interested in studying. A prospective study of PRES would eliminate this problem. Although such a study would take many years to complete, it would be helpful to perform an EEG in all patients who are diagnosed with PRES, providing EEG information for all patients with PRES, including the ones in whom seizures did *not* occur. It might be interesting to know if there are differences in the EEG of people who had seizures and those who did not. For instance, if there is a difference, the EEG information might identify people with PRES who are at *greater risk* for having seizures. Further study of this syndrome is needed. ■

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 solvents has been most closely associated with an increased risk of Parkinson's disease?

a. n-Hexane
b. Xylene
c. Toluene
d. Trichloroethylene

2. Which of the following statements is *false*? The Othello syndrome:

a. is more common in neurological rather than psychiatric conditions.
b. can be drug-induced.
c. is associated with diffuse or focal brain disease.
d. can be reversed by dopaminergic drugs.
e. has been associated with right frontal lobe pathology.

3. Biopsy material in recently diagnosed multiple sclerosis patients shows cortical inflammation that is similar to inflammation present in the white matter lesions.

a. True
b. False

4. Which of the following characteristics is *NOT* associated with muscle complications from statin therapy?

a. Diabetes
b. Stroke
c. Lower body mass index
d. Liver disease
e. Age over 60 years

5. Which of the following is a *true* statement regarding the diagnosis of CLIPPERS?

a. There is a diagnostic biomarker for CLIPPERS.
b. Pathology of CLIPPERS is specific for the disease.
c. Family history is helpful in making the diagnosis of CLIPPERS.
d. The diagnosis requires exclusion of many inflammatory diseases of the nervous system.
e. The cause of CLIPPERS has been defined.

6. Which of the following about posterior reversible encephalopathy syndrome is *NOT* correct?

a. PRES is a syndrome that has many etiologies.
b. Hyperintensities observed on MRI are probably due to vasogenic edema.
c. Seizures are common during the acute PRES episode.
d. Chronic epilepsy often occurs after PRES.
e. Clinical signs associated with PRES usually resolve.

In Future Issues:

Update on Neuromuscular Disease

PHARMACOLOGY WATCH

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

New, Shorter Treatment Regimen for Tuberculosis

In this issue: New treatment for TB; safety of dabigatran; quality of antidepressants; systolic hypertension treatment; and FDA actions.

Short course treatment for latent TB

Three months of two drugs administered once weekly is as effective as 9 months of daily isoniazid (INH) for the treatment of latent tuberculosis infection (LTBI), according to a new study. An international team of researchers randomized nearly 8000 patients with latent tuberculosis (TB) to 3 months of directly observed once-weekly therapy with rifapentine 900 mg plus INH 900 mg or 9 months of self-administered daily INH 300 mg. The primary endpoint was confirmed TB after 33 months of follow-up. In the modified intention-to-treat analysis, TB developed in 0.19% of the once-weekly combination group and in 0.43% of the INH only group. Rates of completion were much higher with the short course, once-weekly regimen (82.1% in the combination-therapy group and 69.0% in the INH only group, $P < 0.001$). Rates of hepatotoxicity were higher in the INH only group. The authors conclude that use of rifapentine plus INH given once a week for 3 months is as effective as 9 months of INH in preventing tuberculosis and has a higher treatment-completion rate (*N Engl J Med* 2011;365:2155-2166). Based on this study and others, the CDC has issued a new recommendation on the use of short-course combination therapy for latent TB infection. The recommendation states, "The new regimen is recommended as an equal alternative to the 9-month INH regimen for otherwise healthy patients ≥ 12 years who have LTBI and factors that are predictive of TB developing (e.g., recent exposure to contagious TB)." It also recommends that the new regimen may be considered for other categories of patients when it offers advantages. Daily INH continues to be the preferred regimen for children between the ages of 2 and 11 (*MMWR Morb Mortal Wkly Rep* 2011;60:1650-1653). ■

Bleeding concerns with dabigatran

Dabigatran (Pradaxa), Boehringer Ingelheim's blockbuster anticoagulant, is the subject of a December 7, 2011, Drug Safety Communication by the FDA regarding serious bleeding events. The FDA is evaluating postmarketing reports of serious bleeding events that may lead to serious or even fatal outcomes. Experts are working to determine whether the reports of bleeding associated with the drug are occurring more commonly than would be expected based on observations from large clinical trials. The drug was approved in October 2010 to reduce the risk of stroke in patients with non-valvular atrial fibrillation. More than a million prescriptions have been filled by nearly 400,000 patients since approval. ■

All antidepressants are created equal

When it comes to choosing an antidepressant, all modern drugs are roughly equivalent, according to a new study in the *Annals of Internal Medicine*. Researchers performed a large meta-analysis of 234 studies that looked at the treatment of major depressive disorder (MDD) with second-generation anti-

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depressants. There were no differences among the drugs with regard to efficacy or effectiveness for the treatment of acute, continuation, and maintenance phases of MDD. There were also no significant differences when accompanying symptoms were taken into account or other factors such as age, sex, ethnicity, or comorbid conditions. There were differences among the drugs with regard to onset of action, adverse effects, and some quality-of-life issues. There was also a significant difference in cost and dosing convenience. Drugs considered in the study were bupropion, citalopram, desvenlafaxine, duloxetine, escitalopram, fluoxetine, fluvoxamine, mirtazapine, nefazodone, paroxetine, sertraline, trazodone, and venlafaxine. The authors suggest that familiarity with the broad spectrum of antidepressants is prudent given the difficulty of predicting which medication will be effective and tolerated by any given patient (*Ann Intern Med* 2011;155:772-785). ■

Benefits of treating systolic hypertension

Older adults with isolated systolic hypertension gained about 5 months of life when treated with chlorthalidone-based stepped care 2 decades after completion of the Systolic Hypertension in the Elderly Program (SHEP) trial. SHEP, conducted between 1985 and 1990, was a clinical trial of patients aged 60 years or older (mean age 72) with isolated systolic hypertension who were randomized to chlorthalidone-based antihypertensive therapy or placebo. Over a mean follow-up of 4.5 years, chlorthalidone-based therapy resulted in prevention of approximately 1 of 2 admissions for heart failure, 1 out of 3 fatal or nonfatal strokes, and 1 of 4 coronary heart disease events, but there was no effect on all-cause mortality or cardiovascular death. At the end of the trial, all participants were advised to receive active therapy. The new study reviewed cardiovascular death and all-cause mortality in SHEP trial participants 22 years after the study ended. Life expectancy gain between the active treatment group and placebo group was 105 days (95% confidence interval [CI], -39 to 242; $P = 0.07$) for all-cause mortality and 158 days (95% CI, 36-287; $P = 0.009$) for cardiovascular death. Each month of active treatment was associated with approximately 1 day extension in life expectancy. The authors conclude that treatment of isolated systolic hypertension with chlorthalidone stepped-care therapy for 4.5 years was associated with longer life expectancy at 22 years of follow-up (*JAMA* 2011;306:2588-2593). This study may help convince older patients with systolic hypertension that compliance with diuretic-based hypertensive therapy is worth the effort as it will prolong their lives. ■

Aliskiren and ACEIs/ARBs don't mix

Aliskiren (Tekturna), Novartis' direct renin inhibitor, should not be combined with an ACE inhibitor or angiotensin receptor blocker (ARB) to treat hypertension, according to the manufacturer. Novartis recently terminated the ALTITUDE trial when it was found that patients with type 2 diabetes or impaired renal function who were given the combination of aliskiren with an ACEI or ARB had a higher incidence of nonfatal stroke, renal complications, hyperkalemia, and hypotension. More information can be found at www.novartis.com/newsroom/media-releases/en/2011/1572562.shtml. ■

FDA actions

The FDA approved generic atorvastatin (Lipitor) on November 30, 2011. Ranbaxy Laboratories will make the first generic in 10, 20, 40, and 80 mg strengths. Atorvastatin as Lipitor was first marketed in 1997 and became the best-selling prescription medication in history with sales of more than $125 billion. It has dominated the statin market in recent years, representing nearly a quarter of Pfizer's annual revenue, and the giant pharmaceutical company aggressively defended their patent against multiple challenges. Ranbaxy has 180 days of exclusivity on generic atorvastatin after which time multiple manufacturers are expected to seek approval for their generic version of the drug.

The FDA has approved Prevnar 13 for adults age 50 and older to prevent pneumonia and invasive disease caused by *Streptococcus pneumoniae*. The vaccine was previously approved for children up to 5 years of age. The approval was based on head-to-head studies with Pneumovax 23 which is already approved for use in adults. According to the FDA, "for the 12 common serotypes, Prevnar 13-induced antibody levels were either comparable to or higher than the levels induced by Pneumovax 23." Prevnar 13 is manufactured by Wyeth Pharmaceuticals.

Dronedarone (Multaq) should not be prescribed to patients with permanent atrial fibrillation (AF), based on results from the PALLAS trial which showed that the drug doubles the risk for cardiovascular death, stroke, and heart failure in such patients. The FDA is requiring revised labeling for the antiarrhythmic drug and has issued a Drug Safety Communication after a safety review was completed. If dronedarone is to be prescribed, the FDA recommends ECGs every 3 months and immediately stopping the drug if the patient is found to be in AF. The drug is indicated to reduce hospitalization for AF in patients in sinus rhythm with a history of non-permanent AF (paroxysmal or persistent AF). Dronedarone is manufactured by Sanofi-Aventis. ■

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

VOLUME 17, NUMBER 2 PAGES 3-4 FEBRUARY 2012

Establishing the CV Safety Profile of ADHD Meds in Children and Young Adults

Source: Cooper WO, et al. *N Engl J Med* 2011;365:1896-1904.

CASE REPORTS OF ADVERSE CARDIOVASCULAR (CV) events in children and young adults taking attention deficit-hyperactivity disorder (ADHD) medications have included myocardial infarction (MI), stroke, and sudden death. These individual cases, however, neither prove causation nor provide insight into event frequency, since the denominator is unknown. Because of the seriousness of these events, a clearer understanding of their epidemiology is important.

Cooper et al performed a retrospective cohort study based on data from four large health plans, which included data from more than 1 million persons 2-24 years of age. Among this population, there were data on 373,667 person-years of ADHD drug treatment in these children and young adults.

In this entire population, there were 81 serious CV events (rate = 3.1/100,000 person-years). However, persons currently using ADHD drugs did *not* demonstrate an increased risk for CV events compared to non-users; in fact, the hazard ratio (HR) demonstrated a trend (not statistically significant) toward *fewer* serious CV events in persons taking ADHD medications (HR = 0.75). Whether CV events were looked at in composite (MI + stroke + sudden death) or individually, the same generally favorable trend was seen (HR = 0.70, *P* = NS). Similarly, former users of ADHD medications were at no greater risk for CV events than never-users. This study was not funded by industry, but by the federal agencies AHRQ and FDA. ■

If You're Already on a Statin, Does Adding Niacin Help?

Source: AIM-HIGH Investigators. *N Engl J Med* 2011;365:2255-2267.

RESULTS FROM INTERVENTION TRIALS WITH statins for secondary prevention of cardiovascular (CV) events are consistently impressive. Nonetheless, significant residual risk remains; that is, even though statin treatment reduces risk of events by as much as 20-30% over 5 years, persons with existing CV disease are still at substantially greater risk of having another CV event than age-matched controls without CV disease. Observational studies suggest that increasing high-density lipoprotein (HDL) might provide an even greater incremental CV risk reduction than LDL modulation, although evidence from interventional trials is conflicting.

The AIM-HIGH trial enrolled patients with existing CV disease (n = 3414) who were already receiving simvastatin (plus ezetimibe if LDL goals were not attained with simvastatin alone). Study subjects were randomized to extended-release niacin or placebo.

Although intended to conclude after 4.6 years, the study was stopped early (at 3 years) subsequent to the recommendation by the data and safety monitoring board that the trial be discontinued due to both a lack of positive efficacy as well as an unanticipated elevation of ischemic stroke in niacin recipients. Adding niacin to statins in persons with stable atherosclerotic vascular disease does not reduce CV events. ■

Adverse Effects on Semen from SSRI Treatment of Premature Ejaculation

Source: Koyuncu H, et al. *Int J Impot Res* 2011;23:257-261.

SEVERAL TREATMENTS HAVE BEEN SHOWN to be highly effective in management of premature ejaculation (pEJ), including behavioral therapy, systemic modulation of serotonin, and topical agents. The most popular current treatment is sustained use of selective serotonin reuptake inhibitors (SSRIs), which typically increase intravaginal latency (the time from intromission to ejaculation) from pretreatment times of < 1 minute to over 5 minutes. There has been little study of the impact of SSRI treatment on parameters such as semen, perhaps because most of the pEJ trials have been short-term. Studies in which SSRIs are added to semen preparations in vitro have shown adverse changes in sperm motility and viability, prompting consideration of potential adverse effects from systemically administered SSRIs.

Escitalopram is an SSRI sometimes used to treat pEJ. To elucidate the effects of escitalopram on semen, subjects with lifelong pEJ (n = 25) and normal baseline semen analysis were enrolled. Additionally, at baseline all subjects had normal scrotal ultrasound, CBC, glucose, hormone levels, lipid levels, and genito-rectal examinations.

At 1 month, no alterations in semen were detected. However, at 3 months there were multiple statistically significant changes: sperm count decreased (68 million/mL to 26 million/mL), number of motile spermatozoa decreased by more than 50%, and the number of morphologically normal sperm decreased by over 50%. In the absence of a control group, these findings cannot be considered definitive. Additionally, it is possible that sperm function might return to pretreatment levels upon drug discontinuation. However, the prominent effects on semen within a short interval merit our awareness. ■

Comparing Two High-Intensity Statin Regimens: Atorvastatin and Rosuvastatin

Source: Nicholls SJ, et al. *N Engl J Med* 2011;365:2078-2087.

Between statin head-to-head trials are uncommon. The PROVE-IT trial convincingly demonstrated that intensive LDL reduction with atorvastatin (achieved LDL = 62 mg/dL) vs pravastatin (achieved LDL = 95 mg/dL) improved outcomes in persons with acute coronary syndromes. In persons with stable atherosclerotic disease, however, it remains controversial whether high-dose statin treatment reduces mortality when compared with "standard" dosages, even though it has been shown to reduce CV events.

Results from clinical trials are sometimes hampered by the limitations of time: In a 5-year window of opportunity, are the long-term effects of intervention adequately represented? Such time limitations have prompted consideration of surrogate markers, which might more promptly reflect the anticipated long-term effects of intervention. Accordingly, Nicholls et al performed a controlled trial (n = 1039) to compare, by means of intravascular ultrasound, the effects of high-dose atorvastatin (80 mg/d) vs rosuvastatin (40 mg/d) on coronary atherosclerosis.

At 2 years, atheroma regression was similar between the two agents, despite the superior performance of rosuvastatin for attained LDL (62.6 mg/dL vs 70.2 mg/dL) and HDL (50.4 mg/dL vs 48.6 mg/dL). Maximal doses of these statins appear to perform similarly for the endpoint of regression of atherosclerosis. ■

The Effect of Adiposity on Insulin Pharmacodynamics

Source: Porcellati F, et al. *Diabetes Care* 2011;34:2521-2523.

It is probably not a surprise to clinicians that adiposity and efficacy of therapeutic insulins are related. We are accustomed to seeing type 2 diabetes (DM2) associated with being overweight and obesity, and watching control of diabetes become more difficult if obesity worsens. The question addressed by Porcellati et al is not whether insulin requirements are affected by obesity, but rather are various insulins differently affected by obesity.

To that end, DM2 subjects (n = 18) were studied using infusions of glucose to maintain constant plasma levels. Three different insulins — NPH, insulin glargine, and detemir — were compared. The threshold at which glucose infusion rates were meaningfully different was a body mass index (BMI) > 29 kg/m^2, at which point all three insulins demonstrated less efficacy to control glucose. That is, as BMI goes up, insulin sensitivity goes down.

Within this study group, however, there was a statistically significantly greater reduction in insulin sensitivity with detemir than with either NPH or insulin glargine. Ultimately, this means that in patients with progressively greater BMI, a higher dose of detemir may be required to achieve glucose control than the other two forms of basal insulin. Some clinical trials have also reflected this requirement for greater doses of detemir than comparators in patients with obesity. Nonetheless, because the amount of data addressing this issue remains small, whether there are meaningful differences that need to be considered when addressing insulin needs of obese DM2 patients in reference to choice of basal insulin is still considered a matter of controversy. ■

Psoriasis Predisposes to Serious Infections

Source: Wakkee M, et al. *J Am Acad Dermatol* 2011;65:1135-1144.

As the use of systemic immune-modulating treatments for rheumatoid arthritis (RA) has evolved, the risk for serious infectious disease complications related to their use has become more evident. Since many of the drugs used to treat RA are now used for patients with psoriasis (PSR), it is logical to evaluate PSR patients for risk of serious infectious diseases.

Wakkee et al looked at a database comprised of PSR patients (n = 25,742) and controls (n = 128,710) from a Dutch registry compiled from 1997-2008. They examined the incidence of infectious disease events resulting in hospitalization during this interval.

Overall, persons with PSR were more than twice as likely to be hospitalized for a serious infectious disease than controls; multivariate analysis (adjustment for confounding issues like age, diabetes, COPD) modified this hazard ratio slightly (down from 2.08 to 1.54).

Perhaps the greatest surprise from this trial was that the use of systemic antipsoriatic medications was *not* associated with risk for infectious disease. Apparently then, it is PSR itself which imposes an increased risk of infectious diseases, not the immunosuppressive agents increasingly used to treat it. ■

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

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