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INSIDE

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Biomarkers and the Diagnosis of Alzheimer's Disease

ABSTRACT & COMMENTARY

By Michael Lin, MD, PhD

Assistant Professor of Neurology and Neurosciences, Weill Cornell Medical College

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

Synopsis: *Biomarkers in the cerebrospinal fluid open the possibility of diagnosing early or even presymptomatic cases of Alzheimer's disease, thereby expanding the potential window for therapy.*

Sources: Bateman RJ, et al. Clinical and biomarker changes in dominantly inherited Alzheimer's disease. *N Engl J Med* 2012;367:795-804.

Blennow K, et al. Effect of immunotherapy with bapineuzumab on cerebrospinal fluid biomarker levels in patients with mild to moderate Alzheimer disease. *Arch Neurol* 2012;69:1002-1010.

Roh JH, et al. Disruption of the sleep-wake cycle and diurnal fluctuation of beta-amyloid in mice with Alzheimer's disease pathology. *Sci Transl Med* 2012;4:150ra122.

REVISED GUIDELINES FOR THE DIAGNOSIS OF ALZHEIMER'S DISEASE (AD), PUBlished last year by the National Institute on Aging and the Alzheimer's Association, place new emphasis on laboratory and imaging biomarkers.[1,2,3] Use of such biomarkers could allow earlier diagnosis, when symptoms are not yet severe enough to meet clinical criteria for AD,[2] or possibly even before symptoms arise.[3] There is gathering consensus that earlier diagnosis may be critical for successful intervention, as damage already may be severe by the time symptoms appear. Three recent papers highlight this new emphasis on biomarkers.

Bateman and colleagues investigated the timing of various biomarker and clinical changes in patients with autosomal dominant familial AD. Patients with a dominantly inherited AD mutation develop AD with 100% penetrance, and the age of onset is typically consistent between generations. The investigators analyzed baseline biomarker and clinical data from 128 members of dominantly inherited AD pedigrees (88 carriers, 40

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noncarriers), and they estimated the time from expected symptom onset based on the parent's age at symptom onset. A characteristic sequence of pathologic changes was found: 1) Cerbrospinal fluid (CSF) Aß42 levels declined as early as 25 years before expected symptom onset; 2) Parenchymal Aß deposition, assessed by PET imaging with Pittsburgh compound B (PiB), was detected 15 years before expected symptom onset. Increased CSF tau levels and hippocampal atrophy were also detected at this time; 3) Glucose hypometabolism and impairment on neuropsychologic memory testing were observed 10 years before expected symptom onset; 4) Decline on Mini-Mental State Exam was detected 5 years before expected symptom onset; 5) Diagnostic criteria for dementia were met 3 years after expected symptom onset. These results support the hypothesis of a characteristic pathophysiologic cascade beginning with changes in Aß, and potentially could form the basis of entry criteria for new trials.

Roh and colleagues investigated the relationship between Aß biomarkers and sleep. The authors had previously shown that synaptic activity induces secretion of Aß, and that Aß levels in brain interstitial fluid (ISF) fluctuate with the sleep/wake cycle. In the current work, they showed that in transgenic mice overexpressing mutant APP and presenilin 1, brain accumulation of Aß with aging is associated with both loss of the diurnal fluctuation in ISF Aß as well as impairment in sleep/wake cycling. Importantly, both the diurnal ISF Aß fluctuations and sleep/wake cycling remained normal if Aß accumulation was prevented by immunizing the mice against Aß. In normal human subjects, they found a similar diurnal fluctuation in CSF Aß concentrations, which was still present in patients who had dominantly inherited AD mutations but no parenchymal Aß deposits (assessed by PET imaging with PiB). In contrast, patients with dominantly inherited AD mutations and parenchymal Aß deposits (assessed by PET imaging with PiB) had loss of the normal diurnal CSF Aß fluctuations. These results suggest that brain Aß accumulation affects both sleep and normal diurnal Aß metabolism, and could be improved by preventing such accumulation. These findings could potentially be highly relevant, given the frequency of sleep disturbance with both aging and AD.

Blennow and colleagues used CSF biomarkers (Aß, phosphotau, and total tau) to monitor response to therapy in two Phase 2, multicenter, randomized, placebo-controlled trials of bapineuzumab, a monoclonal antibody against Aß. Forty-six subjects with mild-to-moderate AD (27 on bapineuzumab, 19 on placebo) were examined over 1 year. Interestingly, there were no clear cut changes in CSF Aß levels compared to baseline. However, CSF phosphotau levels decreased significantly compared to baseline in the bapineuzumab group (-9.9 pg/mL, $P = 0.001$), and this change was significantly larger than that seen in the placebo group ($P = 0.03$). CSF total tau levels also decreased significantly compared to baseline in the bapineuzumab group (-72.3 pg/mL, $P = 0.03$), though the difference between this change and that seen in the placebo group was not quite significant ($P = 0.09$). Given previous evidence that tau pathology likely follows Aß changes, these results suggest that Aß-directed immunotherapy can have effects "downstream" in disease pathogenesis. Unfortunately, the Phase 3 trials of bapineuzumab failed to show benefit in any of the primary clinical endpoints.[4]

■ COMMENTARY

Further work is necessary. For example, the study of Bateman and colleagues on the sequence and timing of biomarker changes was cross-sectional, and results need to be verified by longitudinal follow-up studies. Also, it remains to be seen whether dominantly inherited AD, which accounts for < 1% of cases, is an accurate model for "sporadic" AD. Another important question is what biomarkers, if any, can be used to monitor response to therapy and correlate well with clinical improvement. One interpretation of recent failures in AD therapeutic trials is that it is already too late to intervene by the time symptoms have appeared. If this is true, the only way to intervene presymptomatically will be by having reliable biomarkers for the disease. This will clearly be an active area in the immediate future. ■

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Recognizing a Rare Disorder: Painful Legs and Moving Toes

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, PhD

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

Synopsis: *This case series of patients with painful legs and moving toes is the largest to date and describes association with female gender, peripheral neuropathy and radiculopathy, cancer, and autoimmune disorders. Neurophysiology suggests an additional central component, supporting recruitment of a spinal cord or brainstem generator.*

Source: Hassan A, et al. Painful legs and moving toes syndrome: A 76-patient case series. *Arch Neurol* 2012;69:1032-1038.

THIS CASE SERIES OF INDIVIDUALS WITH PAINFUL LEGS AND moving toes (PLMT) describes patients identified from the electronic medical record database at the Mayo Clinic, Rochester, MN, from 1982-2011. Inclusion required diagnosis documented in the record by a neurologist. In this 18-year period, the 76 cases identified comprised 50 (66%) women, with mean age of onset 58 years (range 24-86 years), of whom 69 (91%) had symptom onset in one or both legs, and 70/74 (95%) reported pain. Pain in both legs and arms was reported in 13%, and the majority, but not all (58%), had bilateral symptoms by the time of evaluation. None had symptoms in the arms only. Descriptions of pain were highly variable and included tingling, numbness, aching, shock, prickly, throbbing, deep, and cold. Involuntary movements, generally occurring some time after onset of pain symptoms, were varied but include wriggling, dystonia, flexion-extension, fanning, clawing, and piano-playing. The authors note medical histories of cancer in 12, hypothyroidism in 11, type 2 diabetes in seven, gastric bypass in three, low vitamin B12 level in five, but no chronic pain syndrome. Taken together, the authors count 24% as having likely autoimmune disorders (coexisting diseases including hypothyroidism, vitamin B12 deficiency, idiopathic thrombocytopenia, primary ovarian failure, and rheumatoid arthritis). Sensory peripheral neuropathy was identified in 48% upon examination, although the authors report nerve conduction abnormalities were "mild," and included radiculopathy, peripheral neuropathy, and other abnormalities. EMG recordings characterized the irregular bursts between 50 msec to 1 sec, and a range of frequency from 2-200 Hz. Most treatments recorded were aimed at pain relief. Although the degree of relief was reportedly moderate or less, 2/3 responded to tramadol, 4/22 to gabapentin enacarbil, 2/9 to pregabalin, and 3/13 to amitriptyline. For control of movement, 3/10 responded to dopamine agonist administration, and 4/17 to clonazepam.

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This is the largest case series reported to date of PLMT, a rare disorder (at the Mayo Clinic, an average of just over four patients were identified per year). Possibly related, and even more rare, conditions are "painful arms and moving fingers" and "painless legs and moving toes." This case series underscores the heterogeneity of the disorder and as such is consistent with previous case series, but serves both to draw attention to the diagnosis and to provide a platform for further study.[1] In practical terms, in patients presenting with lower limb pain, PLMT needs to be considered, and all such patients should be examined with shoes and socks off for involuntary movements. Although, as the authors point out, treatment options appear limited, a diagnosis will help avoid aggressive and potentially inappropriate interventions for pain. Five of these 76 subjects underwent surgery for pain treatment without relief, and in one case a patient underwent multiple laminectomy and fusion procedures without relief. Moreover, at least in

Stroke Alert: A Review of Current Clinical Stroke Literature

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

Thrombolysis for Ischemic Stroke Associated with Cervical Artery Dissection Does Not Improve Overall Outcome

Source: Engelter ST, et al. Thrombolysis in Cervical Artery Dissection — Data from the Cervical Artery Dissection and Iscaemic Stroke Patients (CADISP) database. *Eur J Neurol* 2012;1199-1206.

THE EFFICACY OF THROMBOLYSIS IN ACUTE ISCHEMIC stroke is well established, but in the subset of patients who have a cervical artery dissection, the data are less clear. Thrombolysis could worsen the situation by increasing the intramural hematoma, or it could be beneficial by helping to recanalize the arterial thrombosis at the site of the dissection. In a multicenter European database of 616 patients with cervical artery dissection and ischemic stroke, analysis of outcome at 3 months (modified Rankin Scale 0-2) and occurrence of "major hemorrhage" (any intracranial hemorrhage and major extracranial hemorrhage) was assessed in patients treated with thrombolysis compared to those who were not. This was on open-label, observational study, where all patients were treated according to the wishes of their treating physicians, and the analysis was performed retrospectively.

Out of a total of 616 patients, 68 (11%) received thrombolysis, and of those, 55 (81%) received the intravenous route. Thrombolyzed patients had more severe strokes (median NIHSS score 16 vs 3; $P < 0.001$) and more often occlusion of the dissected vessel (66.2 % v. 39.4%; $P < 0.001$), but after adjustment for stroke severity and vessel occlusion, the chance of favorable outcome was no different between the groups. In matched groups, the odds for good recovery were identical (odds ratio, 1.00; 95% confidence interval, 0.49-2.00). The thrombolyzed group had more serious hemorrhages (5.9% vs 0.6%), but these did not alter outcome or mortality. ■

In Patients with Lacunar Strokes, Addition of Clopidogrel to Aspirin Does Not Reduce Risk of Recurrent Stroke

Source: The SPS3 Trial Investigators. Effects of clopidogrel added to aspirin in patients with recent lacunar stroke. *N Engl J Med* 2012;367:817-825.

SMALL SUBCORTICAL BRAIN INFARCTS, KNOWN AS LACUnar strokes, account for about 25% of all ischemic strokes. They are believed, in most cases, to be caused by disease of small penetrating arteries, i.e., lenticulostriate branches of the middle cerebral arteries, and are the most common cause of "silent" brain infarcts and vascular dementia. Lacunar infarcts were included in studies of intravenous thrombolysis, and they are treated with

these authors' opinions, it may not be necessary to rush to suppress involuntary movements, as they report that patients were more concerned with the pain component of the disorder. The existence of neuropathy and radiculopathy in many of these subjects suggests PLMT may be a peripheral movement disorder, similar to "jumpy stumps," belly dancers' dyskinesia, or hemifacial spasm. However, the authors also point out an overlap with dystonia (some of the subjects' involuntary movements were dystonic in fact) and, in particular, dystonia associated with complex regional pain syndrome. As in prior reports, these cases suggest the possibility that longstanding pain leads to central remodeling, producing the movement disorder component of the disorder. This will await more objective studies, but in the meantime this study is a first step to attempting to dissect out the complexity of PLMT, and brings to our attention the need to consider this diagnosis in patients evaluated for leg pain. ■

Reference

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Neuro-Behçet Disease

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

r-tPA within the appropriate time window. However, secondary prevention of lacunar strokes with antiplatelet therapies has not been specifically studied using MRI as a sensitive method to detect new infarcts.

The Secondary Prevention of Small Subcortical Strokes (SPS3) trial compared two randomized interventions, clopidogrel 75 mg with aspirin 325 mg vs aspirin 325 mg alone in patients who had a lacunar stroke (≤ 2 cm) within 180 days of enrollment. There were 3020 patients enrolled, with a mean age of 63 years, and 63% were men. After a mean follow-up of 3.4 years, the risk of recurrent stroke was not significantly reduced with dual antiplatelet therapy, compared to aspirin alone (2.5% per year vs 2.7% per year). The risk of major hemorrhage was almost doubled with dual antiplatelet therapy vs aspirin alone (2.1% per year vs 1.1% per year; hazard ratio [HR], 1.97). All-cause mortality was increased in the dual antiplatelet therapy group (hazard ratio, 1.52; 95% confidence interval, 1.14-2.04; *P* = 0.004), but this increase in mortality was NOT accounted for by fatal hemorrhages. In patients with lacunar stroke, the addition of clopidogrel to aspirin did not reduce the risk of recurrent ischemic stroke, but did increase the risk of serious bleeding and death. ■

Risk of Restenosis After Carotid Artery Stenting and Carotid Endarterectomy Are Similar

Source: Lal BK, et al, for the CREST Investigators. Restenosis after carotid artery stenting and endarterectomy: A secondary analysis of CREST, a randomized controlled trial. *Lancet Neurol* 2012;11:755-763.

In the carotid revascularization endarterectomy versus Stenting Trial (CREST), the overall results of stroke, myocardial infarction, or death during the periprocedural period did not differ between carotid artery stenting (CAS) and carotid endarterectomy (CEA) for either symptomatic or asymptomatic carotid stenosis. This secondary analysis was aimed to compare the overall risk of restenosis of occlusion.

The study enrolled 2191 patients in CREST from 2000 to 2008, and after randomization to either CAS or CEA, their carotid arteries were assessed with duplex ultrasound at 1, 6, 12, 24, and 48 months. Restenosis was defined as a reduction in diameter of the target artery of at least 70%. The frequency of restenosis was calculated by Kaplan-Meier survival estimates, and proportional hazards models were used to assess the association between baseline characteristics and risk of restenosis.

A total of 1086 patients underwent CAS and 1105 underwent CEA. In 2 years, 58 patients who underwent CAS (6.0%) and 62 who had CEA (6.3%) had restenosis or occlusion (hazard ratio [HR], 0.90; 95% confidence interval, 0.63-1.29; *P* = 0.58). Independent significant predictors of restenosis included female sex (HR = 1.79), diabetes (HR = 2.31), and dyslipidemia (HR = 2.07). Cigarette smoking predicted an increased rate of restenosis after CEA but not after CAS. ■

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

Synopsis: *Behçet's disease, while rare in North America, should be considered when appropriate, in light of the extensive travel and immigration patterns around the world.*

Source: Casanova Peno I, et al. Neurobehcet disease: Clinical and demographic characteristics. *Europ J Neurol* 2012;19:1224-1227.

First described by hippocrates, and characterized by anterior or posterior uveitis, aphthous ulcers, and painful genital lesions, Behçet's disease is a systemic inflammatory perivasculitis, predominantly occurring in the Middle and Far East and Mediterranean basin. Behçet's disease may affect any organ system, including the gastrointestinal tract, the skin and joints, and the large vessels, encompassing both the venous system, the superior and inferior vena cava and dural sinuses, and the arterial system, notably the aortic, carotid, pulmonary, iliac, femoral, and popliteal arteries. Neurologic involvement is more frequent in men than women and may affect the central or peripheral nervous system, but is seen in fewer than 15% of cases. In the absence of any pathognomonic laboratory test, and given the small number of patients reported, little is known of neuro-Behçet disease.

Retrospective review of all medical records of patients discharged from the Hospital Clinico San Carlos, in Madrid, Spain, between 1996-2009, with a diagnosis of Behçet's disease, was undertaken to determine the clinical and demographic characteristics of neuro-Behçet disease. Diagnosis of neuro-Behçet was based on neurological or psychiatric symptoms, with appropriate MRI findings

including intraparenchymal focal lesions, aneurysms, arterial dissections or vasculitis, and/or cerebrospinal fluid abnormalities, encompassing increased cells, protein, or intracranial pressure, in the absence of another possible explanation. Statistical analysis utilized the nonparametric U Mann-Whitney test with $P < 0.05$ considered statistically significant.

Among 25 patients diagnosed with Behçet's disease, seven (28%) fulfilled neuro-Behçet criteria. Two had neuro-Behçet at the time of initial Behçet's disease diagnosis, but in no patient was it the initial symptom. Neurologic manifestations included focal epilepsy in two patients, and one each with a brainstem and cerebellar lesion, and one each with cerebral venous thrombosis, aseptic meningitis, or both. Relapsing-remitting disease was present in all but one, who had a progressive course, and intravenous steroid therapy followed by immunosuppressive medication, including azathioprine, methotrexate, cyclosporine, and infliximab, was beneficial to all. Among the remaining 18 non-neuro-Behçet patients, four each had a primary headache or psychiatric disorder, or nonspecific MRI abnormalities, and two had epilepsy with no evidence of neuro-Behçet. Overall, neuro-Behçet patients had a younger age-of-onset than the non-neuro-Behçet patients, 22.4 years vs 32.88 years, and had a significantly longer evolution until diagnosis, 3.3 years vs 0.35 years. Early suspicion of neuro-Behçet is needed for timely diagnosis and treatment.

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Indications are that Behçet syndrome may not be the same disease worldwide.[1] Distinct regional differences exist, with northern European and American patients demonstrating mild ocular pathology and rare skin-test positivity, compared to severe eye disease seen in the Middle and Far East, and 60% skin-test positivity in countries of the Silk Road. Gastrointestinal disease is rare in Turkey (< 1%), but is seen in up to 50% of patients in Japan and Korea, whereas vascular disease is seen in only 5-10% of cases in the Far East but in 40% in the Middle East. Familial clustering of acne/arthritis cases also argue against one common pathological pathway for all, as does the variable responses of different organ systems to the same medication. Further research will be needed to allow us to fully understand this puzzling disease. ■

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Erythropoietin for Optic Neuritis: Improvements in Structure, but Will Function Follow?

ABSTRACT & COMMENTARY

By Marc Dinkin, MD

Assistant Professor of Ophthalmology, Weill Cornell Medical College

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

Synopsis: *Intravenous erythropoietin therapy appears to reduce retina nerve fiber layer thinning 16 weeks after onset of optic neuritis, but larger studies needed to detect differences in visual outcome.*

Source: Sühs KW, et al. A randomized, double-blind, phase 2 study of erythropoietin in optic neuritis. *Ann Neurol* 2012;72:199-210.

The prognosis for visual recovery in patients with a first episode of optic neuritis is good, with > 95% of patients recovering to better than 20/40 visual acuity at 1 year, with or without treatment with IV methylprednisolone. Yet, the remaining 5% of patients may be left with severe visual loss, and many of those with excellent recovery to 20/20 still complain of disturbing changes in their vision such as trouble with low contrast or peripheral field defects. Furthermore, with repeated attacks of optic neuritis, incremental small, but permanent, changes in vision ultimately can result in significant impairment. It is therefore imperative that new therapies are identified that will protect the optic nerves and improve visual outcome in these patients. Unfortunately, although the optic neuritis treatment trial (ONTT) demonstrated a faster speed of recovery in optic neuritis patients who receive IV methylprednisolone, visual acuity, color vision, and visual fields were not significantly altered by the medication. Perhaps with this in mind, Sühs et al report on a prospective, double-blind, placebo-controlled trial evaluating the effects of a putative neuro-protective agent, erythropoietin, on patients with optic neuritis, not yet diagnosed with multiple sclerosis (MS). In addition to stimulating red blood cell formation, erythropoietin has been shown to have some neuroprotective properties in animal models of MS and optic neuritis and, importantly, can cross the blood-brain barrier when given systemically.

In this study, the authors gave standard methylprednisolone plus 33,000 units of IV recombinant human eryth-

ropoietin to 21 patients in the experimental arm, while the 19 control patients received methylprednisolone plus placebo. The primary outcome measure was the degree of thinning of the retinal nerve fiber layer (RNFL) at 16 weeks, as measured by optical coherence tomography (OCT), reflecting the growing recognition that the axonal loss reflected in thinning of this unmyelinated layer is associated with permanent changes in visual function in all manners of optic nerve injury. Changes in optic nerve diameter measured by MRI, delay of P100 on visual evoked potential (VEP), and visual acuity and fields were secondary outcome measures.

The authors found that RNFL thicknesses, which normally average around 100 μm, decreased by a median of 7 μm (to 3.5 μm less than the unaffected eye) in the erythropoietin group vs 17 μm (7 μm less than the unaffected eye) in the placebo group. MRI showed a drop of 0.1 mm in optic nerve diameter in the placebo group, and none in the treated group. VEP latencies were shorter in the treated group (median of 113.15 ms) than the placebo group (132.73 ms). There was no difference in visual acuity or automated fields.

■ COMMENTARY

In the nearly 20 years since the ONTT, this study represents the first prospective, double-blinded, placebo-controlled trial of a neuroprotective agent as a treatment for optic neuritis. The results are exciting, as they appear to indicate a significant reduction in the degree of RNFL thinning in those who received erythropoietin. The limitation of the treatment is of course that there was no significant effect on either visual acuity or fields, and some therefore might question the drug's value for this condition at all. However, as it has been shown that acuity drops begin to be irreversible when a certain threshold of RNFL thinning (< 75 μm) occurs, it stands to reason that the patients who received erythropoietin, were, on average, left with that much more cushion against significant vision loss, should another episode of optic neuritis ensue in the future. Furthermore, it is conceivable that these patients' color vision and low contrast visual acuity (LCVA), which have been shown to correlate well with RNFL thickness, may have been better preserved in the erythropoietin patients. For this reason, it is disappointing that the authors did not test these parameters as part of this study.

The positive results of this study must be tempered by the recognition that the mean baseline VEP latency was longer in the placebo group (153.54 ms vs 139.88 ms), suggesting that optic neuritis was, on average, more severe among those who did not receive erythropoietin. Prior studies have shown that more severe cases of optic neuritis have a worse prognosis for full recovery, so this may have confounded the results. Furthermore, their observation that MRI-determined reduction in optic nerve diameter was less in the erythropoietin group may have simply reflected the fact that the degree of initial optic nerve thickening was higher (by approximately 150%) in the placebo group. Finally, as the authors point out, one of the patients in the placebo group demonstrated a very high degree of initial RNFL thickening (> 100 μm more than the fellow eye). The subsequent reduction in that initial edema, while counted as RNFL "thinning," in fact mostly reflects a resolution of thickening. When the authors removed that patient, the remaining *P*-value was barely significant.

Despite these limitations, this study presents a strong argument for further testing of erythropoietin as a therapy for optic neuritis and offers hope that it may pan out as the first treatment to significantly affect the outcome in this disease. With larger sample sizes, they may more convincingly demonstrate sparing of the RNFL, and most importantly, a reduction of ensuing vision loss in these patients. ■

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. All of the following are true regarding cerebrospinal fluid (CSF) biomarkers and Alzheimer's disease (AD), *except* for:

a. CSF Aß42 levels decline in the CSF many years before symptoms are apparent in AD.

b. CSF tau levels are increased in AD.

c. PET imaging with Pittsburgh compound B is always diagnostic of AD.

d. Hippocampal atrophy, determined by MRI, occurs before symptoms in AD.

e. Sleep disorders are common in patients with AD.

2. Which of the following is correct regarding "painful legs and moving toes" syndrome?

a. It is a classical example of a psychogenic disorder.

b. It purely involves the lower extremities and never affects the arms.

c. Its associated symptom of pain is exquisitely responsive to dopamine agonist treatment.

d. It is often associated with peripheral neuropathy.

e. Mechanisms are thought to be purely of peripheral nervous system origin.

3. Which of the following may be seen with Behçet syndrome?

a. Focal epilepsy

b. Relapsing remitting disease

c. Cerebral venous thrombosis

d. Aseptic meningitis

e. All of the above may be seen with Behcet syndrome

4. Intravenous methylprednisolone for acute optic neuritis improves the long-term prognosis for preserved vision.

a. True

b. False

5. Thrombolysis for acute ischemic brain infarcts, in the setting of cervical artery dissection, has been proven to be beneficial.

a. True

b. False

6. The addition of clopidogrel to aspirin, in order to prevent recurrent ischemic stroke, has no additional risks.

a. True

b. False

7. The risk of restenosis of the carotid artery after carotid artery stenting or carotid endarterectomy is about the same.

a. True

b. False

In Future Issues: **Neurological Complications of Reproduction**

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Refining the Relationship Between Thyroid Hormones and Left Ventricular Mass

Source: Iida M, et al. *J Am Soc Hypertens* 2012;6:261-269.

Animal studies have shown that thyroid hormones (T3 and T4) induce hypertrophy of cardiac myocytes through stimulation of both structural and regulatory myocyte genes, which can be prevented by ACE inhibitors or beta-blockers. Such observations have led to the question of whether there might be a relationship between cardiac mass and thyroid hormones, even within the range currently defined as normal.

Hypothyroidism and hyperthyroidism are each considered a potential secondary cause of hypertension: the former through endothelial dysfunction that leads to vasoconstrictor hyperresponsiveness and subsequent increased peripheral resistance, and the latter through increased sympathetic tone. Iida et al investigated hypertensive subjects (n = 293) who had no known thyroid disease and whose thyroid function tests (T3, T4, and TSH) were within normal limits.

Among these euthyroid hypertensive study subjects, multiple linear regression found a positive relationship between T3 and T4 and ventricular mass (the higher the thyroid hormones, the greater the ventricular mass), and an inverse relationship between TSH and ventricular mass. When compared with normotensive controls, no such relationship could be identified. This would lead to consideration that in persons with hypertension, higher levels of thyroid hormone — even within the normal range — may be related to the development of left ventricular hypertrophy. ■

The ORIGIN Trial: Basal Insulin vs Standard Care for Early Type 2 Diabetes

Source: The ORIGIN Trial Investigators. *N Engl J Med* 2012;367:319-328.

Type 2 diabetes reflects insulin insufficiency. Early in the disease process, plasma insulin levels may actually be higher than normal, but insufficient to maintain euglycemia. By the time of formal diagnosis, approximately half of beta cell mass has been lost, and as the disease progresses, insulin levels continue to fall.

The Outcome Reduction with an Initial Glargine Intervention (ORIGIN) trial randomized subjects with prediabetes or early diabetes (n = 12,537) to insulin glargine (GLAR) or standard treatment (STND) for 6.2 years (mean). The objective of the trial was to determine whether early institution of basal insulin, as compared to STND, improves cardiovascular outcomes. Standard treatment was simply treatment of diabetes as per the treating clinician's choice; by the end of the trial, only 11% of the STND group was receiving insulin. Eighty percent of the GLAR group was on insulin at the end of the trial.

There was no difference in cardiovascular outcomes between the two treatment groups. One notable difference between treatments was the likelihood of progression from prediabetes to diabetes. The GLAR group was 28% less likely to progress than the STND group; however, there was also more hypoglycemia and weight gain in the GLAR group.

Increased incidence of cancer — a concern generated by earlier insulin trial data — was *not* seen in this large trial, and hence should be very reassuring. ■

Bronchodilators in COPD and Arrhythmias

Source: Wilchesky M, et al. *Chest* 2012; 142:298-304.

For chronic obstructive pulmonary disease (COPD), except for the provision of oxygen in late-stage disease, no pharmacologic intervention has been confirmed to save lives. Nonetheless, since bronchodilators improve symptoms, quality of life, and exercise capacity, and reduce acute exacerbations of COPD, they play an important role in routine care. Concerns about the potential capacity for arrhythmogenicity of bronchodilators has arisen from clinical COPD trials such as the Lung Health Study (n = 5887), in which short-acting ipratropium bromide was associated with a three-fold greater incidence of arrhythmia than comparator groups. Other smaller trials have not confirmed these findings, hence clarification is needed.

Wilchesky et al analyzed data from the province of Saskatchewan, Canada, to identify COPD subjects (n = 6018) and compare the incidence of arrhythmia in new users of ipratropium, beta-agonists (short- and long-acting), and methyhlxanthines to non-users.

Short-acting anticholinergics were

associated with a 2.4 relative risk of arrhythmia, and long-acting beta-agonists with a 4.5 relative risk. No statistically significant increased risk was seen with short-acting beta-agonists or methylxanthines. Despite these concerns, the authors remind us that the absolute risk increase was very small, and "in most cases would be outweighed by the therapeutic benefit accrued through symptomatic relief and consequent improvements to quality of life." ■

Reversible Dementia from Corticosteroid Therapy

Source: Cipriani G, et al. *Clin Geriatrics* 2012;20:38-41.

Although there are many clinical situations in which corticosteroids (CTS) are disease modifying and life saving, one aspect of CTS that has not received much attention is the potential for central nervous system (CNS) adverse effects. CTS may be largely subgrouped into mineralocorticoids exemplified by aldosterone, and glucocorticoids (GLC) like prednisone, the latter of which is the object of this case report.

There are at least two types of CTS receptors in the brain: type I (mineralocorticoid receptors) and type II (glucocorticoid receptors). Type II receptors are found in the hippocampus as well as diffuse other sites throughout the brain. The hippocampus is required for voluntary recollection of learned information, such as recalling what you had for dinner last night. Even low doses of GLC have been shown to impair hippocampal function, despite being used for short time periods: doses of prednisone of 80 mg/day have been shown to alter cognitive function within 4-5 days.

The authors include discussion of a report detailing six cases of dementia-like cognitive decline (distinct from steroid psychosis) in patients whose cognitive function was restored upon GLC discontinuation.

Clinicians should be vigilant for decline in cognitive function in persons receiving GLC treatment, even over the short-term. ■

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Could Thinner be Worse for Newly Diagnosed Diabetics?

Source: Carnethon MR, et al. *JAMA* 2012;308:581-590.

Usually, we anticipate a direct relationship between overweight and cardiovascular adversity, attributed to increases in blood pressure, lipids, glucose, insulin resistance, and sympathetic tone that are associated with obesity. There appears to be some exception to this general rule in reference to diabetes. For instance, in the TRIAD study, diabetics who were normal weight at entry to the study had a *higher* mortality than overweight/obese study subjects; similarly, in the PROactive trial, normal weight subjects or those who lost weight had *higher* mortality than overweight subjects. Because these two studies included confounding issues such as diabetes of varying duration and pre-existing cardiovascular disease, a more clear-cut relationship between body mass index (BMI) and outcome in diabetes could be discerned by selecting newly diagnosed diabetics.

Carnethon et al performed a pooled analysis of five longitudinal cohort studies (n = 2625) to examine the relationship between mortality and BMI for persons with newly diagnosed diabetes. Overall, only 12% of study subjects had a BMI < 25 at the time of diagnosis, but the relative risk for total mortality during follow-up (up to 15 years) was essentially doubled in this population compared to overweight individuals.

The mechanism(s) by which lower BMI increases mortality risk are unknown. Clinicians must not be falsely reassured that this lower-BMI phenotype, which is commonly seen in Asian-Americans, portends a favorable future. ■

The Impact of Exercise on Depression in Heart Failure

Source: Blumenthal JA, et al. *JAMA* 2012;308:465-474.

It is estimated that 5 million Americans have chronic heart failure (CHF), and almost half of these patients fulfill diagnostic criteria for depression. Subsyndromal depression is present in as many as 75%. Notwithstanding the burden of depression on quality of life, a direct impact on mortality has been shown in post-myocardial infarction patients, and even in patients with hypertension in the Systolic Hypertension in the Elderly Program. Unfortunately, to date the information on the impact of treating depression is both limited and generally disappointing. For instance, a clinical trial of sertraline in depressed patients with CHF found no cardiovascular event outcomes benefit.

Exercise is a treatment for depression, and exercise has been shown to provide event reduction in CHF patients. Whether it might improve depression and cardiovascular events in CHF patients was the object of the HF-ACTION trial (Heart Failure-A Controlled Trial Investigating Outcomes of Exercise Training).

More than 2000 patients with stable CHF were randomized to an aerobic exercise program. The exercise subjects enjoyed a statistically significant 11% reduction in mortality over the next 30 months. Although the mean score on the Beck Depression Inventory was statistically significantly lower in the exercise group, the improvement was sufficiently modest to be of uncertain clinical impact. Exercise in CHF reduces mortality and may have a modest effect on depression. ■

PHARMACOLOGY WATCH

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Statins and Cognition — More to the Story?

In this issue: Side effects of statins; effects of cannabis use; antihypertensives and lip cancer; and FDA actions.

Review challenges FDA warning

Do statins cause changes in cognition? In February, the FDA added warnings to statin labels regarding the risk of reversible memory loss and confusion. But a new review from the *Journal of the American College of Cardiology* reviews the evidence given to the FDA and concludes "that there is no increased risk of cognitive decline" with statin use. The State-of-the-Art Paper was a comprehensive review of case reports, observational research, and randomized, controlled trials of statins and cognitive change, as well as risk of cancer and diabetes. Most of the evidence for cognitive changes came from individual case reports, many of which were self-reported by consumers to the FDA. Observational studies gave mixed results on cognition with four of nine studies showing statins improved cognition, while three showed no change, and two studies found an increased risk of cognitive impairment. The authors suggest that these studies are inconclusive and prone to selection bias. Two large, randomized, controlled clinical trials specifically looked at the effect of statins on cognitive function as the major secondary endpoint. In both, no significant differences were seen between the study and control groups with regard to cognitive decline. Twelve smaller studies showed mixed results with the majority showing no change and only one in 12 showing a detrimental effect of statins on cognitive function, while two studies showed a benefit. Along with lack of evidence to suggest statins lead to cognitive decline, the authors also found no evidence that statins increase the risk of cancer. They did, however, find a small risk for development of diabetes, which they felt was "outweighed by the cardiovascular benefits in patients for whom statin therapy is recommended" (*J Am Coll Cardiol* published online August 15, 2012). ■

Cannabis use and cognitive decline

Persistent cannabis use — particularly in adolescence — may lead to permanent cognitive decline, according to a new study. Researchers looked at a birth cohort of 1037 healthy individuals in New Zealand who underwent neuropsychological testing in the mid 1980s before the onset of cannabis use, and then again in 2010-2012 after some had developed a persistent pattern of cannabis use. Persistent cannabis use over 20 years (at least 4 days per week) was associated with neuropsychological decline, with greater decline evidence for more persistent users. This effect was only seen in adolescent-onset cannabis users and was associated with an average 8 point loss in IQ by age 38. The effect persisted after controlling for education, other drugs, or tobacco. The effects were not seen among adult-onset cannabis users. The authors conclude that increasing efforts should be directed toward delaying the onset of cannabis use by young people, "particularly given the recent trend of younger ages of cannabis use initiation in the United States and

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evidence that fewer adolescents believe that cannabis use is associated with serious health risk." (*Proc Natl Acad Sci U S A* published online August 27, 2012). This study and others are increasingly important as cannabis, the most widely used illicit drug in the world, is being considered for more medicinal uses as well as legalization. ■

Antihypertensives and lip cancer

Two photosensitizing antihypertensives, hydrochlorothiazide and nifedipine, may increase the risk for lip cancer in non-Hispanic white patients, according to a new study from Kaiser Permanente in California. From a large cohort of patients, 712 were identified with lip cancer along with nearly 23,000 matched controls. At least a 5-year supply of the drug resulted in the following odds ratios for lip cancer (95% confidence intervals) — hydrochlorothiazide 4.22 (2.82-6.31), hydrochlorothiazide-triamterene 2.82 (1.74-4.55), nifedipine 2.50 (1.29-4.84), and lisinopril 1.42 (0.95-2.13). When atenolol was given without other hypertensives, the odds ratio for lip cancer was 0.54 (0.07-4.08). The authors suggest that while antihypertensive therapy outweighs the risk of lip cancer, preventive measures should be taken for those at increased risk because of fair skin and long-term sun exposure (*Arch Intern Med* published online August 06, 2012). ■

FDA actions

The FDA has approved a delayed-release form of prednisone for the treatment of endocrine, inflammatory, and neoplastic conditions. Delayed-release prednisone should be taken once a day with timing to be determined by the disease being treated. For example, 10 p.m. dosing is recommended for rheumatoid arthritis, as it is more effective than immediate-release prednisone taken in the morning for treating morning stiffness associated with the disease. Dosing is based on the theory that both cytokines and endogenous cortisol follow a circadian rhythm, and that dosing the drug based on the condition being treated may afford more effective treatment than immediate-release prednisone. The new product delays the release of prednisone by approximately 4 hours. Side effects are the same as short-acting prednisone. Delayed-release prednisone will be marketed as RAYOS by Horizon Pharma.

The FDA has approved a new chlorofluorocarbon (CFC)-free, over-the-counter inhaled racepinephrine product for the treatment of asthma. The new product takes the place of the banned Primatene Mist, which was taken off the market at the end of 2011 because it contained CFCs. Inhaled epinephrine has been used for the treatment of asthma for more than 100 years. Marketed as Asthmanefrin, the new product will be sold as a starter kit and refill package. The starter kit will include 10 vials of racepinephrine along with the EZ Breathe Atomizer. The refill kit will include 30 vials of the drug. The drug is not without controversy, however, with many asthma experts feeling that the side effects of epinephrine are serious and well-documented, and over-the-counter use goes against published guidelines for treating asthma. Asthmanefrin will be marketed by Nephron Pharmaceuticals.

The FDA has approved linaclotide for the treatment of chronic idiopathic constipation and irritable bowel syndrome with constipation. The drug is the first guanylate cyclase (GC-C) agonist that acts locally in the gut with minimal systemic exposure. The drug is taken once daily on an empty stomach at least 30 minutes before the first meal of the day. Safety and efficacy in the management of irritable bowel syndrome with constipation was established in two double-blind studies of nearly 1300 patients who were randomly assigned to linaclotide or placebo for 12 weeks. Patients taking the drug experienced more complete spontaneous bowel movements than those taking placebo. The drug should not be used in patients 17 years or younger. Linaclotide will be jointly marketed by Ironwood Pharmaceuticals and Forest Pharmaceuticals as Linzess.

Montelukast (Singulair), Merck's popular asthma and allergy medication, will soon be available as a generic. The leukotriene receptor antagonist will be manufactured by 10 generic companies in tablet form, oral granules, and chewable tablets. The FDA warns that montelukast should not be used for relief of sudden asthma attacks and further warns that patients should contact a clinic immediately if they are experiencing behavior and mood-related changes such as aggression, depression, or hallucinations.

The FDA has approved the first generic version of pioglitazone (Actos). The drug is approved along with diet and exercise to improve blood sugar control in adults with type 2 diabetes. This happens as thiazolidinediones have generally fallen out of favor for use in type 2 diabetes due to side effects including worsening heart failure and edema. The FDA also recently issued a warning for pioglitazone regarding increased risk of bladder cancer if the drug is taken for more than 1 year. The first generic pioglitazone will be manufactured by Mylan Pharmaceuticals. ■