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INSIDE

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Neurology of Sjögren's Syndrome

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Peripheral and central nervous system involvement is common in Sjögren's syndrome, and may mimic multiple sclerosis or neuromyelitis optica.*

Source: Gono T, et al. Clinical manifestations of neurological involvement in primary Sjögren's syndrome. *Clin Rheumatol* DOI 10.1007/s10067-010-1458-7.

INITIALLY DESCRIBED BY SWEDISH OPHTHALMOLOGIST HENRIK SJÖGREN (1899-1986), and his wife, also an ophthalmologist, Sjögren's syndrome (SS) is a rare autoimmune disease, with a prevalence of 0.09 to 3.5%, characterized by dry eyes and dry mouth, xeropthalmia, and xerostomia, due to chronic lymphocytic and plasma cellular infiltration of exocrine glands. It exists as a primary disorder, but may co-exist as a secondary disorder in association with other autoimmune conditions such as systemic lupus erythematosus (SLE), dermatomyositis, scleroderma, or rheumatoid arthritis (RA). Primary SS (pSS) may be associated with peripheral or central nervous system involvement, and this retrospective study evaluated pSS patients to determine the variety of these complications in pSS.

Between August 1, 1992 and October 31, 2008, 32 patients with pSS were admitted to Tokyo Women's Medical University, Institute of Rheumatology.

It is with great sadness that we inform our readers that Dr. Fred Plum, emeritus editor of *Neurology Alert* for more than 25 years, has died at the age of 86. Dr. Plum was one of the great leaders in American neurology. He trained at New York Hospital-Cornell Medical Center under Dr. Harold Wolf and became chairman of the department of neurology at Cornell in 1963, holding that position until his retirememt in 1998. His research centered on disorders of consciousness, and he described, in collaboration with Dr. Jerome Posner, many of the syndromes that we now diagnose. Their classical textbook, *The Diagnosis of Stupor and Coma*, initially published in 1966, recently released a 4th edition, and inspired many medical students, including this one, to pursue a career in neurology. Many of his trainees went on to become leaders in neurology and will pass his knowledge down to other generations of trainees. Dr. Plum was a special individual who will be missed by all of us. — *Matthew E. Fink, MD, Editor in Chief*

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Weill Cornell Medical College

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A monthly survey of developments in neurological medicine from the faculty of Weill Cornell Medical College and NewYork-Presbyterian Hospital.

Diagnosis of pSS was based on the revised European criteria of the American-European Consensus Group. Patients with other collagen vascular diseases, including RA, SLE, or scleroderma, were excluded. All patient's charts were reviewed for findings on neurologic examination, magnetic resonance imaging, electroencephalography, and spinal fluid analysis. Fisher's exact test provided statistical analysis and $P<0.05$ was considered significant.

Among the 32 pSS patients, 20 demonstrated neurological involvement. Mean age at diagnosis was 44.2 years for those with, and 46.2 years for those without, neurologic findings, and females predominated in both groups, 95% and 100%, respectively. Neurologic involvement preceded pSS diagnosis in 25%. Other than the presence of fever in those with neurological involvement, no other factor differentiated the groups, including skin rash, lymphadenopathy, antibody positivity (ANA > 160, anti-SS-A, anti-SS-B), or serum immunoglobulin G (IgG) values. Peripheral nervous system (PNS) findings encompassed cranial neuropathy in 41% (n = 7), including optic neuritis (n =3), trigeminal neuralgia (n =2), and one each with facial neuropathy and combined glossopharyngeal and vagus neuropathy. Peripheral neuropathy was seen in 53% (n = 9), purely sensory in eight, with one patient demonstrating sensorimotor neuropathy. Mononeuritis multiplex was seen in 18% (n =3). Central nervous system (CNS) involvement included encephalopathy (n = 3), aseptic meningitis (n = 2), and subclinical white matter changes in the brain and spinal cord (n = 1). Neuromyelitis optica, associated with pSS, was diagnosed in one optic neuritis patient, based on anti-aquaporin 4-antibody positivity. Both CNS and PNS findings occur in pSS but their etiology remains uncertain.

■ COMMENTARY

Peripheral nervous system involvement occurs in approximately 20% of patients with Sjögren's Syndrome. CNS disease is less common. Among 424 pSS patients, diagnosed by the revised European criteria of the American-European Consensus Group, CNS involvement was detected in 25 (5.8%), including 24 females and 1 male, a mean of 7 years following initial diagnosis (*Rheumatology* doi:10.1093/rheumatology/keq111). Diffuse CNS disease was seen in 10 patients (40%), usually manifested by recurrent subacute encephalopathy (n = 6), characterized by impaired concentration, attention, and cognition, memory loss, visual disturbances, and dizziness. Focal or multifocal disease was seen in 9 patients (36%), and encompassed focal motor deficits, aphasia, seizures, parkinsonism, and cerebellar ataxia. Multiple-sclerosis-like disease was seen in five patients (20%) and isolated optic neuritis, seen in a single patient (4%), rounded out the most common CNS presentations. Whereas articular manifestations were more common in pSS patients without neurological complications, significant risk factors for CNS disease included pulmonary involvement, decreased complement (C4) level, and longer pSS duration, with lung disease emerging as the strongest association. ■

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Questions & Comments
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Monoclonal Gammopathy and the CNS

ABSTRACT & COMMENTARY

By Russell L. Chin, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr. Chin reports no financial interest in this field of study.

Synopsis: *Nine of nineteen patients with monoclonal gammopathy, referred for evaluation of peripheral neuropathy, were found to have one or more clinical signs of CNS involvement.*

Source: Lehmann HC, et al. Central nervous system involvement in patients with monoclonal gammopathy and polyneuropathy. *Eur J Neurol* 2010; doi:10.1111/j.1468-1331.2010.02977.x

In this case series, nineteen patients (9 men, 10 women) with M-protein, referred for suspected peripheral neuropathy, were evaluated consecutively over a four-year

period. Sixteen patients had monoclonal gammopathy of unknown significance (MGUS), one patient had "chronic lymphatic leukaemia" and two patients were diagnosed with plasmacytoma. The M-protein was IgG in10 patients, IgM in eight patients, and IgA and IgM in one of each. Four patients with IgM M-protein had ganglioside antibodies (including to GD1a, GD1b, GM1, GA1, and MAG). Peripheral neuropathy was diagnosed by clinical and electrodiagnostic examination in 17 patients (nine sensorimotor, five sensory, three motor).

Nine of the 19 patients had potential CNS involvement with one or more of the following clinical signs: tremor (5 patients), dysarthria (4), ataxia (4), extensor plantar responses (3), and nystagmus (1). Three of the 10 patients who had cranial MRI studies had extensive multifocal leukoencephalopathy that could not be attributed to age or small vessel disease. Diluted sera from two patients with IgM M-protein stained neurons of the cortex and cerebellum of paraffin-embedded human brain tissue. In the cortex, there was intense staining of axons and cell bodies in the grey and white matter. In the cerebellum, there was intense staining of granular cells with sparing of Purkinje cells. No staining was observed with sera containing IgG M-protein or normal serum. Disease duration was significantly longer in patients with clinical signs of CNS involvement. Serum M-protein was significantly increased in patients with IgM M-protein and signs of CNS involvement.

■ COMMENTARY

Monoclonal gammopathy has been linked to the development of peripheral neuropathy and is associated with conditions such as monoclonal gammopathy of undetermined significance (MGUS), multiple myeloma (including osteosclerotic myeloma), Waldenström macroglobulinemia (also known as lymphoplasmacytic lymphoma), primary systemic amyloidosis and cryoglobulinemia. Careful assessment for these underlying conditions is important given potential therapies, ranging from observation to rituximab, IVIG, steroids, alkylating agents, or radiation therapy.

The IgM monoclonal gammopathies are often associated with anti-nerve antibodies such as myelin-associated glycoprotein (MAG) and glycolipids such as sulfoglucuronyl paragloboside and various gangliosides. Anti-MAG neuropathy is most frequently associated with a slowly progressive, demyelinating sensory neuropathy that may respond to rituximab therapy. Neuropathies associated with IgG or IgA monoclonal gammopathies have a more heterogenous clinical presentation, including a chronic inflammatory demyelinating polyneuropathy-like syndrome. Screening for osteosclerotic myeloma is warranted in these patients. Anti-nerve antibody activity, if found, is of unclear significance. The target antigens of circulating M-protein, however, are not confined to the peripheral nervous system. In this article, sera from two patients with IgM monoclonal gammopathy stained neurons of the cortex and cerebellum, corroborating another report of antibodies reactive against glycolipids in the CNS white matter.[1]

CNS involvement has long been suspected, given the observation of tremor and ataxia in 40% to 90% of patients with IgM paraproteinemic neuropathy. The other features of dysarthria and nystagmus highlighted in this article also implicate CNS (specifically cerebellar) involvement. Tremor is mostly seen in the upper extremities and has characteristics of an enhanced physiologic tremor that is increased with posture and action and typically without a resting component. A central etiology is suspected particularly in the absence of a deafferented state where there would be significant loss of large fiber sensory input. Deep brain stimulation of the VIM thalamic nucleus has also been reported to result in improvement of the tremor associated with an IgM monoclonal gammopathy and demyelinating peripheral neuropathy. As stated in this paper, ataxia is attributed to cerebellar dysfunction (rather than to peripheral sensory loss) when there are features of a lurching gait, with no or only minimal worsening with elimination of visual feedback.

Radiologic findings supporting CNS involvement include the presence of extensive white matter changes not attributable to age and microvascular disease.[1] Enhancing perivascular and subcortical white matter changes have also been reported in a patient with Bing-Neel syndrome,[2] a rare condition of lymphoplasmacytic infiltration of the CNS in patients with Waldenström macroglobulinemia. ■

References

1. Leger JM, et al. Frequency of central lesions in polyneuropathy associated with IgM monoclonal gammopathy: An MRI, neurophysiological and immunochemical study. *J Neurol Neurosurg Psychiatry* 1992;55:112-115.
2. Malkani RG, et al. Bing-Neel syndrome: An illustrative case and a comprehensive review of the published literature. *J Neurooncol* 2010;96:301-312.

Statins Do Not Appear to Slow the Progression of Alzheimer's Disease

ABSTRACT & COMMENTARY

By Michael Lin, MD

Dr. Lin is Assistant Professor of Neurology at Weill Cornell Medical College

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

Synopsis: *In this large, well-powered, prospective, randomized trial, treatment of Alzheimer's patients with a high-dose statin did not have a significant effect on cognitive decline.*

Source: Feldman HH, et al., on behalf of the LEADe Investigators. Randomized controlled trial of atorvastatin in mild to moderate Alzheimer disease: LEADe. *Neurology* 2010;74;956-964.

In the recently published LEAD study (Lipitor's Effect in Alzheimer's Dementia), Feldman and colleagues examined the safety and efficacy of atorvastatin in patients with mild to moderate Alzheimer's disease (AD). This was an international, multicenter, double-blind, randomized, placebo-controlled trial in which 640 subjects with AD (age 50-90, MMSE 13-25, LDL 95-195 mg/dL, no significant cardiac or cerebrovascular disease) were randomized to atorvastatin (80 mg/day) or placebo for 18 months, followed by a two-month washout period.

Treatment with atorvastatin produced a 72 mg/dL drop in LDL, compared to a 1 mg/dL drop in the placebo group. However, there was no significant difference compared to placebo in either cognition or global function as primary endpoints, measured by the AD Assessment Scale-Cognitive subportion and the AD Cooperative Study Clinical Global Impression of Change. A volumetric MRI substudy in 10% of subjects showed a significant smaller annualized decrease in hippocampal volume with atorvastatin, but the MRI subsample was not representative of the whole study; there were significant differences in baseline demographics between treatment arms, and a significant effect on ADCS-CGIC favoring atorvastatin, neither of which was present in the entire study. Treatment with atorvastatin was safe. Of note, there were no adverse cognitive effects, despite anecdotal reports of cognitive impairment with statins. In fact, at every time point after baseline, the ADAS-Cog score was slightly (but not significantly) better in the atorvastatin group.

This study provides class II evidence that intensive lipid lowering therapy in mild to moderate AD does not benefit either cognition or global function. It is the largest and longest randomized, double-blind, placebo-controlled trial of statins in AD to date. The sample size afforded at least 80% power to detect a 30% to 40% effect in either primary endpoint at 18 months with a two-tailed test, assuming dropout of up to 30%. All the assumptions made in study design were met, including the rate of cognitive decline in the placebo group, the dropout rate, and the degree of cholesterol lowering.

On the other hand, one limitation of the study is that subjects were excluded if there was a definite indication for use of a statin, or any significant cardiovascular or cerebrovascular disease. It is possible that AD subjects with higher LDL levels or more significant vascular disease may have shown a greater degree of benefit.

■ **COMMENTARY**

This study continues the saga concerning the role of statins in AD prevention or therapy. In cultured cells and transgenic mice, cholesterol modulates Aβ production, and statins reduce Aβ production. In retrospective case-control studies, statins are associated with reduced risk of AD. However, prospective epidemiologic studies have been mixed, and two large randomized cardiovascular prevention trials with cognition as secondary endpoints have not shown any benefit. Another large clinical trial of a statin in AD (simvastatin) was reported to be negative at an international meeting, but formal publication is pending.

Based on this study, use of statins solely as treatment for AD is not indicated. Their effects on AD, when given for vascular or lipid-lowering indications, remain to be seen, and their role in prevention is still unclear. ■

Multiple Sclerosis: The Eyes Have It

ABSTRACT & COMMENTARY

By Marc Dinkin, MD

Assistant Professor of Ophthalmology, Weill Cornell Medical College

Dr. Dinkin reports no financial interest in this field of study.

Synopsis: *Pathological study shows atrophy within the inner nuclear layer of the retina and uveal tract inflammation in eyes from patients with multiple sclerosis*

Source: Green A, et al. Ocular pathology in multiple sclerosis: Retinal atrophy and inflammation irrespective of disease duration. *Brain* 2010;133:1591-1601.

In a landmark study in *Brain*, Ari Green and colleagues reported on the largest ocular pathology series in patients with multiple sclerosis. A total of 132 eyes of 82 patients were compared with 16 eyes of patients with other neurological disease and analyzed with haematoxylin and eosin staining, while a subset of eyes were stained for astrocytes, inflammatory cells and tight junctions. The authors found that 79% of eyes in the MS group showed

atrophy of the retinal nerve fiber layer (RNFL) and retinal ganglion cells (RGC) vs. only 19% of control eyes, confirming prior pathological studies and a plethora of clinical studies utilizing optical coherence tomography (OCT). Furthermore, 29% of eyes of relapsing-remitting or secondary-progressive MS patients showed peri-venular cellular infiltrates in the RNFL and RGC layers. While the presence of retinal periphlebitis has been demonstrated in prior pathological studies and in some clinical cases, the authors made the novel finding that this inflammation was independent of disease duration, confirming that retinal involvement is not a rare, late finding in MS.

The most salient finding of the study was prominent atrophy in the inner nuclear layer of 40% of MS eyes vs. 0% controls, with a sparing of the outer nuclear layer, answering the longstanding question of how deeply the retina is affected by the disease. The authors make a strong argument that atrophy of the inner nuclear layer is based on trans-synaptic degeneration since it correlated with RGC loss, the latter of which was always more prominent, and since it never occurred in cases of acute MS.

While uveitis has rarely been associated with clinical MS, the authors showed that 72% of MS eyes contained some combination of iris stromal inflammation, pupillary margin pigment layer eversion and iris neovascularization, vs. only 25% of controls. The authors theorize that such changes result from a distressed retina since vascular changes correlated with retinal atrophy, although a direct effect on the uveal tract remains a possibility.

Finally, optic nerve head analysis demonstrated a high prevalence (70%) of perivenular gliosis, with variable effects on the architecture of the nerve, confirming findings of prior studies.

■ COMMENTARY

This study benefits not only from its status as the largest ocular pathological study of MS, but from the fact that the bulk of patients died prior to the advent of disease-modifying agents, so that the findings are likely to reflect MS in its untreated state. The categorization of patients into subtypes of MS allowed the authors to demonstrate differences such as the relative scarcity of perivascular inflammation in the primary progressive patients. The inclusion of an "other neurological disease" control group strengthened the study, although it should be noted that the disease duration in this control group was considerably shorter than in the MS group. As mentioned, the authors' discovery of inner nuclear layer atrophy and uveal tract inflammation in a significant proportion of MS patients makes a great contribution to our understanding of the extents of MS' effect on the eye and non-myelinated structures in general. Furthermore, the presence of retinal inflammation and gliosis may help inform our interpretation of layer segmentation in patients with MS in the future.

The study was limited by the dearth of clinical data in the study patients. Most importantly, there was no clinical data on the frequency of optic neuritis in the MS patient population so conclusions could not be made regarding the relative effect on the retinal elements by serial episodes of optic nerve inflammation vs. the chronic background effects of the disease. Clinical data on the prevalence of anterior ocular disease would have been informative in light of the high frequency of iris neovascularization and stromal inflammation observed pathologically.

The observation of "frequent" optic nerve cupping in the study patients corresponds poorly with clinical observations that demyelinating optic neuropathies lead to temporal pallor and ultimately a flat and atrophic disc. The finding is particularly difficult to interpret because the authors did not specify its actual frequency, and because pathological cupping was defined as any excavation or indenting of the optic disc. The low stringency of this definition would likely include a good proportion of the aged population, since while only 1%-2% of patients in the UK have definite glaucoma, a much greater proportion have physiologic cupping and are labeled as glaucoma suspects. Clinical comparison of optic nerve cupping in multiple sclerosis patients compared with aged-matched controls might help confirm or repudiate this relatively controversial pathological finding. Finally, as the authors point out, findings in one pathological area of an eye might have unblinded investigators to some extent as they searched for pathology in other tissues.

These critiques aside, this study has clearly broken new ground in definitively establishing atrophy and inflammation in the inner nuclear layer of the retina and within the iris. Its findings are sure to contribute greatly to our understanding of the pathophysiology of multiple sclerosis and inspire further investigations into its effect on the retina and surrounding ocular structures. ■

Medical Therapy Alone vs Addition of Deep Brain Stimulation in Advanced PD

ABSTRACT & COMMENTARY

By Panida Piboolnurak, MD and Michael G. Kaplitt, MD, PhD

Dr. Piboolnurak is Assistant Professor, Department of

Neurology and Neuroscience, Weill Medical College, Cornell University.

Dr. Kaplitt is Associate Professor and Vice-Chairman for Research, Department of Neurological Surgery, Weill Medical College, Cornell University

Neither Dr. Piboolnurak nor Dr. Kaplitt reports any financial relationship relevant to this field of study.

Synopsis: *Deep brain stimulation (DBS) is an effective treatment in Parkinson's disease with motor fluctuations and dyskinesias. However, given the potential adverse events, proper patient selection is vital.*

Source: Williams A, et al. Deep brain stimulation plus best medical therapy versus best medical therapy alone for advanced Parkinson's disease (PD SURG trial): Randomized, open-label trial. *Lancet Neurology* 2010;9:581-591.

In this randomized, open-label trial, the investigators recruited 366 patients with Parkinson's disease (PD) who did not have an adequate benefit from medications. Patients were randomly assigned to a group treated with medication and surgery, or medical therapy alone. Of the total, 178 patients had surgery (174 had subthalamic nucleus DBS, and four had globus pallidus interna DBS), and 171 patients had only medical therapy (12 patients switched over to DBS after the assignment). Dyskinesia and severe "off" periods were the most common reasons for considering surgery.

Patients' self-evaluating, 39-item, PD questionnaire summary index improved by 5 points in the surgical group and by 0.3 point in the medical group. There was no evidence that the degree of improvement in favor of surgery varied with age, disease duration, Hoehn & Yahr stage, reason for surgery, or whether apomorphine treatment was planned. Total Unified Parkinson's Disease Rating Scale (UPDRS) score in the "on-medication" state improved by 6.6 points in the surgical group, but worsened by 1.6 points in the medical group. Total UPDRS score in the "off-med" state improved by 27.4 points in the surgical group and by 0.9 points in the medical group. Of note, patients in the surgical group were evaluated while DBS was on in either the "on-med" or "off-med" state. At one year, 75 patients in the surgical group had no dyskinesia and 45 reported no "off" time. On the contrary, 21 patients in the medical group had no dyskinesia, and five reported no "off" time.

Dementia Rating Scale Score decreased by 0.4 points in both groups. Only a subset of patients had detailed neuropsychological evaluation. Utilizing the Delis-Kaplan executive function system, phonemic mean score and verbal fluency decreased by 6.5 and 4.5 points in the surgical group, and by 0.6 and 0.2 point in the medical group. Wechsler abbreviated scale of intelligence vocabulary reduced by 1.5 point in the surgical group, but improved by 0.6 point in the medical group. Patients in the surgical group required 34% less medication compared to the patients in medical group. At baseline, 45 patients in each group were on apomorphine. By one year, this had decreased to 13 (six with continuous infusion) in the surgical group, but had increased to 63 (48 with continuous infusion) in the medical group. Thirty-six patients in the surgical group had 43 surgery-related serious adverse events, of which infections were the most common. There were 25 PD-related or drug-related serious adverse events in 20 patients in the surgical group and 14 events in 13 patients in the medical group. One patient who had previously attempted suicide before the study had an unsuccessful suicide attempt after the surgery. Two patients in the surgical group died (intraoperative hemorrhage and preoperative pneumonia). One patient in the medical group died from stroke.

■ COMMENTARY

In keeping with previous studies, this study showed that DBS can reduce dyskinesia, "off" duration, and medication requirement. A combination of DBS and best medical therapy was more effective than best medical therapy alone. However, this study was not designed to compare the benefit of DBS to medical therapy, because they did not compare the UPDRS scores in the "on-med" state in the medical group to the scores in the "off-med/on-stim"

CME Objectives

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

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

CME Instructions

- Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.
- After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

state in the surgical group. This is an academic consideration, however, since the goal of therapy is to optimize patient quality of life and the combination of DBS and best medical therapy was clearly superior in this particular patient population. Given the well-documented potential for adverse events from surgery, proper patient selection remains very important. In general, DBS is recommended in a patient with motor fluctuation, increasing "off-times" and/or disabling tremors, with or without dyskinesias, who is no longer adequately responding to previously effective medical treatment and who has no significant cognitive deficit or uncontrollable psychiatric disorders that are unrelated to their PD medications. Limitations of this study include an open-label design, limited number of patients with a detailed neuropsychological evaluation, and lack of data on adverse events that were not serious enough to require or prolong hospitalization. ■

CME QUESTIONS

53. Sjögren's Syndrome is associated with:

a. optic neuritis.

b. trigeminal neuralgia.

c. facial neuropathy.

d. purely sensory peripheral neuropathy.

e. All the above

54. **Patients with IgM monoclonal gammopathy may have the following symptoms and signs, *except* for:**

a. Peripheral sensory neuropathy

b. Peripheral motor neuropathy

c. Cerebellar tremor

d. Ataxia

e. Cognitive impairments

55. **The LEADe Study demonstrated that:**

a. statins slow the decline of cognition in AD.

b. statins significantly lower LDL.

c. statins reduce brain atrophy in AD.

d. statins cause cognitive impairment.

56. The following are true of Green et al's findings of ocular pathology in MS *except*:

a. Some degree of iris neovascularization, pigment layer eversion, or stromal inflammation was seen in a majority of eyes of patients with MS.

b. The presence of perivenular inflammation was independent of disease duration.

c. Atrophy of bipolar and horizontal cells in the inner nuclear layer was observed in 40% of eyes of patients with MS and was found independently of disease duration.

d. The outer nuclear layer of the retina was spared in patients with MS.

e. None of the above are true

57. Which statement concerning treatment of advanced Parkinson's disease is *incorrect*?

a. Treatment with DBS alone is more effective than medical therapy.

b. A combination of DBS and medical treatment provided a greater benefit compared to the best medical therapy alone.

c. Most common post-operative serious adverse events were surgery-related infections.

d. DBS should be considered in a patient with motor fluctuation without or with dyskinesia.

58. Aortic arch and descending aorta plaques may be a source of embolic material that can cause ischemic stroke.

a. True

b. False

59. Endovascular thrombectomy is contraindicated after the administration of IV TPA.

a. True

b. False

60. Paroxysmal atrial fibrillation is very rarely discovered in ischemic stroke.

a. True

b. False

61. Aspirin and clopidogrel may be used safely together for 30 days after TIA.

a. True

b. False

Answers: 53. e, 54. e, 55. b, 56. e, 57. a, 58. a, 59. b, 60. b, 61. a

Stroke Alert: A Review of Current Clinical Stroke Literature

***By Matthew E. Fink, MD**, Interim Chair and Neurologist-in-Chief, Director, Division of Stroke & Critical Care Neurology, Weill Cornell Medical College and New York Presbyterian Hospital*

Harloff A, et al. Complex plaques in the proximal descending aorta: An underestimated embolic source of stroke. *Stroke* 2010;41:1145-1150.

Atherosclerotic plaques in the aortic arch are considered to be a potential source of embolism to the brain and a cause of some ischemic strokes, but the role of complex plaques (> 4 mm thickness, ulcerated, superimposed thrombi) in the proximal descending aorta (DAo) is uncertain. The investigators studied 94 consecutive patients who had aortic plaques > 3 mm in thickness in the aortic arch by transesophageal echocardiography, and studied the location and plaque morphology with MRI. They also measured 3-D aortic blood flow to determine if diastolic retrograde flow connected the plaque location to the origins of the great vessels of the aortic arch. Increased flow reversal was correlated with decreasing heart rate ($p < 0.02$) and retrograde flow reached the left subclavian artery in 58%, the left common carotid artery in 25% and the brachiocepahlic trunk in 14%. Using clinical classification of stroke types, potential embolization from DAo plaques could explain embolism in all brain territories and might be the cause of stroke in 25%-33% of patients. ■

Shi ZS, et al. Endovascular thrombectomy for acute ischemic stroke in failed intravenous tissue plasminogen activator versus non-intravenous tissue plasminogen activator patients. *Stroke* 2010; 41:1185-1192.

Intracranial thrombectomy is an option to treat patients with acute ischemic stroke who have a large vessel occlusion. The investigators compared results and complications of the MERCI device in 305 patients, 48 who failed IV TPA and 257 who were ineligible for IV TPA. Non-responders to IV TPA had similar rates of revascularization and less mortality (28% vs 40%) than the non-TPA group, and they had similar rates of symptomatic hemorrhage and procedural complications. Favorable outcomes at 90 days were similar in both groups, with no difference based on the site of occlusion. In both groups of patients, good outcomes were more frequent in revascularized patients. In the non-TPA group, revascularization correlated with good outcome (47% vs 4%) and less mortality (28% vs 60%).

The risks of hemorrhage and procedural complications after mechanical thrombectomy are not different in patients who receive IV TPA compared to those who do not, and this mode of therapy should be considered in IV TPA failures. After thrombectomy, good outcomes are correlated with successful revascularization. ■

Gaillard N, et al. Detection of paroxysmal atrial fibrillation with transtelephonic EKG in TIA or stroke patients. *Neurology* 2010; 74: 1666-1670.

Paroxysmal atrial fibrillation (PAF) is often underdiagnosed after stroke. Long-term monitoring studies suggest that as many as 15% of ischemic stroke patients may have PAF if monitored continuously for up to 12 months. The investigators studied 98 consecutive patients with a clinical diagnosis of non-cardioembolic stroke, using transtelephonic EKG monitoring (TTM), if they had a negative 24-hour Holter monitor. Seventeen PAF episodes were detected in 9.2% (9/98) of the patients, with estimated duration of PAF episodes ranging from four to 72 hours. Two predictors of PAF were identified: > 100 premature atrial ectopic beats on 24-hour Holter monitor ($OR = 11.0$, $p < 0.007$) and nonlacunar anterior circulation DWI signals on MRI ($OR = 9.9$, $p < 0.004$). In patients who had both predictive criteria, detection of PAF occurred in 43% of patients. TTM and other methods of long-term EKG monitoring should be considered in patients with cryptogenic stroke, especially of they have premature atrial contractions on Holter, and DWI signals in the anterior circulation. ■

Geraghty OC, et al. Low risk of rebound events after a short course of clopidogrel in acute TIA or minor stroke. *Neurology* 2010; 74:1891-1896.

The combination of aspirin and clopidogrel is standard therapy for treatment of acute coronary syndrome, and early cessation of clopidogrel has been associated with a rebound in coronary events. A similar effect is unknown in patients with TIA or minor stroke, but this question will be studied in upcoming clinical trials. The investigators looked at this question in an open-label, non-randomized observational study of 320 patients who were prescribed a 30-day course of aspirin 75 mg and clopidogrel 75 mg after TIA or minor stroke. Recurrent events were ascertained at face-to-face follow-up. There were five recurrent ischemic strokes and 7 TIAs during the aspirin and clopidogrel treatment, but no strokes and four TIAs during the 30 days after stopping clopidogrel. Compared to a group of 487 patients who were treated with aspirin alone, there was a similar trend, with 12 recurrent strokes in the initial period and five strokes in the subsequent 30 days. The findings in both groups are consistent with the known history of early recurrent strokes after TIA, but cessation of clopidogrel does not appear to induce a rebound effect. However, this question will only be definitively answered in a larger, randomized trial that is being started shortly (POINT). ■

In Future Issues:

Advances in Movement Disorders

Clinical Briefs in Primary Care™

The essential monthly primary care update

By Louis Kuritzky, MD

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

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Coronary Calcium Scores enhance risk prediction

Source: Polonsky TS, et al. *JAMA* 2010; 303:1610-1616.

PROBABLY THE MOST WIDELY RECOGNIZED scoring system for predicting CV risk is the Framingham Risk Score (FRS). The United States Preventive Services Task Force (USPSTF) has recently published the opinion that novel risk markers such as C-reactive protein do not sufficiently enhance risk prediction enough to justify their routine utilization in addition to traditional scoring systems like FRS Coronary Calcium Score (CCS) has a number of appealing attributes that suggest consideration as a powerful prediction tool.

In the Multi-Ethnic Study of Atherosclerosis (MESA) trial of persons without known CHD at baseline, a CCS > 300 was associated with a 10-fold increased risk for CHD events. A critical issue, however, is whether new or additional prediction score tools add meaningfully to existing methods. A metric known as Net Reclassification Improvement (NRI) has been recently proposed to distinguish whether the incremental impact of a scoring system or risk factor upon already existing methods is meaningful.

Using the cohort of MESA (n = 6814 adults; age > 45), Polonsky et al compared risk prediction as derived from FRS vs FRS + CCS. The addition of CCS to FRS resulted in a statistically significant NRI. An additional 23% of persons who experienced CHD events but had not been identified by FRS as high risk were correctly reclassified by the addition of CCS. Similarly, an additional 13% of subjects not classified by FRS as low risk (and who did not suffer events), were reclassified as low risk by the addition of CCS. Whether the preferential (or additional) use of CCS for risk prediction can improve outcomes over traditional risk scores alone will require further definition, although many are already sufficiently encouraged by the predictive power of CCS to currently employ it. ■

Exacerbations of COPD: Not so innocent

Source: Donaldson GC, et al. *Chest* 2010;137:1091-1097.

ACUTE EXACERBATIONS OF COPD (AE-COPD) are sometimes misconstrued as minimally consequential "bumps in the road" along the journey of progressive COPD. Unfortunately, the toxicity of ae-COPD has been underappreciated; ae-COPD are associated with hospitalizations, loss of lung function that is typically not regained, and mortality. Donaldson et al direct our attention to a newly recognized additional burden of morbidity associated with ae-COPD: MI and stroke.

The Health Improvement Network (THIN) database contains anonymized medical records of patients seen by GPs in England and Wales. Over a 2-year period, 25,857 COPD patients provided a dataset with which to compare the incidence of MI and stroke during "stable" periods of COPD with the immediate post-ae-COPD period.

The incidence of acute MI was increased more than 2-fold in the 5-day period immediately following an ae-COPD; similarly, stroke incidence was increased more than 2-fold in the 49-day period immediately post-ae-COPD. Both findings were statistically significant.

No pharmacologic treatment of COPD has been proven to be disease-modifying. Yet, since various pharmacotherapies have been shown to reduce ae-COPD, perhaps such treatments will ultimately be shown to impact disease outcome by affecting the above-mentioned consequences of ae-COPD: increased stroke and MI. ■

Vitamin E, but not pioglitazone, improves NASH

Source: Sanyal AJ, et al. *N Engl J Med* 2010;352:1675-1685.

STEATOSIS IS THE ACCUMULATION OF FAT, derived primarily from triglycerides in hepatic cells. Progressive steatosis can lead to hepatic inflammation, which, when not associated with alcohol, is known as non-alcoholic steatohepatitis (NASH). Obesity and diabetes are the two conditions most commonly associated with NASH. Because as many as 15% of NASH cases may ultimately progress to cirrhosis, effective treatments are eagerly sought.

Since the pathologic underpinnings of NASH often include insulin resistance, hypetriglyceridemia, and type 2 diabetes, pharmacology with thiazolidinediones (TZD) appears logical. Unfortunately, results from pilot trials of TZDs have been conflicting.

The NASH Clinical Research Network, established by the NIDDK, conducted a

placebo-controlled trial of pioglitazone or vitamin E in non-diabetic NASH patients (n = 247). Subjects received 800 IU/d vitamin E, 30 mg/d pioglitazone, or placebo for approximately 2 years. The primary outcome was histologic status of NASH.

At 96 weeks, vitamin E did demonstrate a statistically significant rate of NASH histologic improvement, but pioglitazone did not. Even though there were some favorable histologic effects, neither intervention showed a reduction in hepatic fibrosis, so we remain uncertain about whether vitamin E can impact the development of serious long-term liver disease. Pioglitazone did not achieve an effect on the primary outcome, but explanations for why TZDs may still be considered for NASH therapy are presented by the authors. ■

Best use of home BP monitoring

Source: Pickering TG, et al. *J Am Soc HTN* 2010;4:56-61.

The largest body of information guiding treatment of hypertension (HTN) is based upon office BP management. Nonetheless, home BP monitoring (HBPM) is documented to be a better predictor of CV risk than office BP. For instance, patients with high office BP but low HBPM are recognized to be at substantially lower risk than office BP predicts; similarly, high HBPM pressures compared to office BP portends greater risk than indicated by office BP alone. Simply the fact that HBPM offers the opportunity for many more BP readings than is readily accessible in clinical care provides both a more comprehensive and consistent BP profile.

Recording HBPM twice daily (morning and evening), when averaged over 1 week, provides a sufficient BP profile to help guide management. By HBPM, HTN is > 135/85 mmHg and normotension is < 125/75 mmHg. Borderline HBPM (125-135/75-85 mmHg) merits consideration of 24-hour ambulatory BP monitoring for further clarification. The authors, writing on behalf of the American Society of Hypertension, provide a list of validated home BP monitoring devices at: www.dableeducational.org/. ■

Suicide risk with anticonvulsants

Source: Patorno E, et al. *JAMA* 2010;303:1401-1409.

Although the term "anticonvulsant" is indicative of a therapeutic class, pharmacologically the class is diverse. Despite dissimilarities, an analysis by the FDA (2008) discerned a relative doubling of suicide behavior/ideation in anticonvulsant recipients compared to placebo, resulting in a change in labeling.

The HealthCore Integrated Research Database provides data with which to assess the relative risk for suicidal acts in persons receiving a variety of anticonvulsant agents. During a 5-year interval (2001-2006), almost 300,000 new prescriptions for various anticonvulsants were documented in this population. When compared to treatment with either topiramate or carbamazepine (reference drugs), important distinctions emerged in reference to suicidal acts and violence. For instance, the hazard ratio for suicidal acts was 1.42 for gabapentin, 1.84 for lamotrigine, and 1.65 for valproate, compared to topiramate.

The mechanism by which some anticonvulsants incur an increased suicide risk is not known, despite the recognition that anticonvulsants can have impact upon mood. The first 2 weeks after initiation is recognized to be a higher risk period. Clinicians should be vigilant for behavior or mood changes in patients treated with anticonvulsants, noting lesser apparent risk for topiramate or carbamazepine. ■

For type 2 diabetes, after metformin, what next?

Source: Phung OJ, et al. *JAMA* 2010;303:1410-1418.

In the absence of contraindications, metformin is the preferred initial treatment for most patients with type 2 diabetes (DM2). Unfortunately, monotherapy is unlikely to maintain adequate glycemic control, requiring additional treatment. Although the addition of insulin to metformin is an appropriate next step, and has been labeled Tier 1 in the most recent guidelines published by the American Diabetes Association, some patients are reluctant to use insulin, and the considerable weight gain experienced by some insulin users, as well as risk of hypoglycemia, is problematic.

Among the non-insulin therapeutic choices, there is a great degree of variation in tolerability issues, such as amount of weight gain and frequency/severity of hypoglycemia that may help guide treatment decisions. Phung et al analyzed data from 27 randomized controlled trials (n = 11,198), most of which were 6 months or less in duration, to compare weight changes and hypoglycemia when non-insulin agents were added to metformin.

As might be anticipated, when TZDs, sulfonylureas, and glinides were added to metformin there was a 1.8-2.1 kg weight gain. GLP-1 mimetics, alpha-glucosidase inhibitors, and DPP-4 inhibitors were either weight neutral or associated with minimal weight loss. Sulfonylureas were associated with higher rates of hypoglycemia.

Of course, progressive treatment of DM2 must be individualized, and should include consideration of characteristic tolerability issues such as weight gain and hypoglycemia. ■

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PPIs, *Clostridium difficile*, and Bone Fractures

In this issue: *New reports about proton pump inhibitors and the effects of gastric suppression, pioglitazone vs vitamin E for non-alcoholic steatohepatitis, metformin and vitamin B12 deficiency, and FDA Actions.*

PPIs, C. difficile, and bone fractures

Since H2 antagonists were introduced 30 years ago followed by proton pump inhibitors (PPIs) 20 years ago, there has been speculation whether long-term gastric acid suppression might have adverse effects. Billions of doses later, there is new evidence that chronic PPI use may lead to infections, especially *Clostridium difficile* infection (CDI), and may also contribute to bone fractures.

In the first of several studies published in the May 10 issue of *Archives of Internal Medicine*, researchers looked at more than 101,796 discharges from a tertiary care medical center during a five-year period, reviewing the level of acid suppression therapy and its relationship to CDI. As the level of acid suppression increased, the risk of CDI increased from 0.3% in patients not receiving acid suppressive therapy to 0.6% in those receiving H2 antagonists to 0.9% in those receiving daily PPIs and finally 1.4% in those receiving high-dose PPI therapy. After adjustment for a number of factors including comorbid conditions, age, and antibiotic use, the odds ratio for CDI infections were: 1 with no acid suppressing treatment, 1.53 (95% confidence interval [CI], 1.12-2.10) with H2 antagonist, 1.74 (95% CI, 1.39-2.13) with PPIs, and 2.36 (95% CI, 1.12-2.10) with high-dose PPI therapy. The authors conclude that increasing levels of pharmacologic acid suppression are associated with increased risk of nosocomial *C. difficile* infections, and the risk increases with more aggressive acid suppression (*Arch Intern Med* 2010;170: 784-790).

In a second study from the same journal, researchers from the VA system in Massachusetts performed a retrospective, cohort study of 1166 inpatients and outpatients with CDI to determine if PPI use affected recurrence rates. During treatment for CDI, 45% of patients received a PPI while 55% did not. Recurrent CDI was more common in those exposed to PPIs than in those not exposed (25.2% vs 18.2%). The hazard ratio for recurrent CDI in those exposed to PPIs was 1.42 (95% CI, 1.11-1.82). The risk was higher in patients older than 80 years and in patients exposed to antibiotics not targeted to CDI infections The authors conclude that PPI use during treatment for CDI was associated with a 42% increased risk of recurrence (*Arch Intern Med* 2010;170:772-778).

It has also been postulated that suppressing gastric acid may affect digestion and absorption of certain nutrients, specifically calcium. Although this has never been definitively proven, multiple studies have shown that chronic PPI use is associated with bone fractures. The most recent study, also published in the May 10 issue of *Archives of Internal Medicine*, was a prospective analysis of more than 160,000 women enrolled in the

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Women's Health Initiative study. In more than 1 million person-years of follow-up, there were 1500 hip fractures, 4881 forearm or wrist fractures, 2315 clinical spine fractures, and more than 21,000 total fractures. The multivariate-adjusted hazard ratios for current PPI use was 1 for hip fracture, 1.47 (95% CI, 1.18-1.82) for clinical spine fracture, 1.26 (95% CI, 1.05-1.51) for forearm or wrist fractures, and 1.25 (95% CI, 1.15-1.36) for total fractures. Bone mineral density did not vary between PPI users and non-users. The authors conclude that use of PPIs in women was not associated with hip fractures but was modestly associated with clinical spine, forearm or wrist, and total fractures (*Arch Intern Med* 2010;170:765-771). This study confirms the findings of several large epidemiological studies that suggest that PPI use is associated with increased osteoporotic fracture risk. On May 25, the FDA issued a warning regarding the possible fracture risk associated with high-dose long-term use of PPIs. The Agency will require labeling changes to describe the possible risk.

As noted in these studies, PPI use is associated with risk of osteoporotic fractures and *Clostridium difficile* infections. Other studies have linked the PPIs to a higher risk of hospital- and community-acquired pneumonia, as well as enteric infection such as *Salmonella* and *Campylobacter* gastroenteritis. In an editorial in the May 10 issue of *Archives of Internal Medicine*, Mitchell Katz, MD, notes that of the more than 110 million prescriptions for proton pump inhibitors filled each year, many are for inappropriate indications, making PPIs one of the most overprescribed medication classes in the world. He suggests that "for most patients the adverse effects of PPIs outweigh the benefits" and urges physicians to offer other treatments for dyspepsia, prescribe shorter courses, and consider a trial of discontinuing PPIs in patients who are asymptomatic (*Arch Intern Med* 2010;170:747-748). ■

Pioglitazone vs vitamin E for NASH

Non-alcoholic steatohepatitis (NASH) is a common liver disease that is difficult to treat and often progresses to cirrhosis. A new study compares the thiazolidinedione pioglitazone (30 mg daily) to vitamin E (800 IU daily) in a placebo-controlled trial for 96 weeks in 247 nondiabetic NASH patients. The primary outcomes were standardized scores for steatosis, lobar inflammation, hepatocellular ballooning, and fibrosis as determined by liver biopsy. Vitamin E therapy was associated with a significant improvement in non-alcoholic steatohepatitis (43% vs 19%; $P = 0.001$), but pioglitazone did not show statistical improvement (34% vs 19%; $P = 0.04$). Serum transaminases improved with both treatments, and both reduced hepatic steatosis and lobular inflammation, but neither improved fibrosis. Pioglitazone caused significant weight gain compared to vitamin E or placebo. The authors conclude that vitamin E was superior to placebo for the treatment of NASH in adults without diabetes (*N Engl J Med* 2010;362:1675-1685). ■

Metformin and vitamin B12 deficiency

Monitor your patients on metformin for vitamin B12 deficiency. This is the message of a recent study from the Netherlands. The study enrolled 390 patients with type 2 diabetes on insulin and initiated metformin 850 mg three times a day or placebo for an average of 4.3 years. Metformin treatment was associated with a mean decrease in vitamin B12 concentrations of 19% ($P < 0.001$) and an increase in homocysteine concentrations of 5% ($P = 0.091$). Longer-term treatment with metformin was associated with larger declines in vitamin B12 levels. The authors conclude that metformin likely causes malabsorption of vitamin B12 and recommends routine monitoring of vitamin B12 levels in patients who are treated with metformin (*BMJ* 2010;340:c2181). ■

FDA actions

The FDA has approved a new formulation of oxycodone (OxyContin®) that is designed to discourage chewing, crushing, or dissolving the drug. The FDA admits, however, that although the new formulation reduces the risk of snorting or injecting the drug, it can still be abused by simply ingesting larger doses than recommended. Vocal critics have called for oxycodone's withdrawal from the market due to an explosion in abuse of the drug nationwide and calls this new formulation "too little too late."

The FDA has recommended resuming use of Rotarix® rotavirus vaccine and to continue using RotaTeq® rotavirus vaccine. Rotarix was found to have elements of the porcine circovirus 1 (PCV1) in March, which resulted in an advisory to clinicians to stop using the vaccine. Subsequently, DNA from PCV1 and PCV2 was discovered in the RotaTeq vaccine. The FDA now says that there is no evidence that PCV causes illness or infection in humans while the benefits of the vaccine are substantial. ■