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Fabry Disease and Small Fiber Neuropathy

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: *Fabry disease, while rare across the general population, is not rare as a cause of small fiber neuropathy.*

Source: Tanislav C, Kaps M, Rolfs A, et al. Frequency of Fabry disease in patients with small-fibre neuropathy of unknown aetiology: A pilot study. *Eur J Neurol* doi:10.1111/j.1468-1331.2010.03227.x

MOST OFTEN A CONSEQUENCE OF DIABETES OR ALCOHOLISM IN THE UNITED States, small fiber neuropathy (SFN) is a common cause of morbidity. But despite aggressive investigations, the etiology for SFN remains undiagnosed in up to 40% of patients. Fabry disease, a rare X-linked lysosomal disorder due to α-galactosidase A (α-GAL A) enzyme deficiency, may cause small fiber neuropathy early in its course. What is the prevalence of Fabry disease in this patient population?

In a retrospective study, undertaken at the Justus Liebig University Department of Neurology, Geissen, Germany, 29 patients evaluated between January 2005 and July 2009, and diagnosed with idiopathic small fiber neuropathy, were contacted and invited to undergo genetic analysis to identify the presence of an α-GAL gene mutation, which required venipuncture and urinalysis, the latter to measure protein level and globotriaosylceramide (Gb3). In selected patients, gluteal skin biopsy was performed to detect Gb3 accumulation. Inclusion criteria mandated documentation of small fiber neuropathy by quantitative testing or skin punch biopsy, normal conventional nerve conduction studies, and negative workup for common causes of small fiber neuropathy, including glucose tolerance test and glycosylated hemoglobin; liver, kidney, and thyroid function; serum protein and immunofixation electrophoresis; glycolipid and glycoprotein antibody screening; antinuclear and antineutrophil cytoplasmic antibody testing; and vitamin B_{12} and folate levels. Patient interviews were screened

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for alcoholism. Statistical analysis, due to the paucity of cases, was limited to calculation of median values and absolute range, with absolute frequencies and proportions used to analyze discrete variables.

Of 29 patients identified with idiopathic small fiber neuropathy, five either could not be reached or refused to participate, leaving 24 patients as the subjects of this study. Median age was 57.1 years (range 29.7 to 70.1 years), and 71% (n = 17) were women. Mutation of the α-GAL gene was demonstrated in five women, of which one mutation was typical and four were found to have a complex heterozygote intronic haplotype within the gene. Increased Gb3 concentrations were found in these four, but its relevance to Fabry disease pathogenesis is otherwise unclear. Fabry disease should be considered in the evaluation of patients with idiopathic painful small fiber neuropathy.

■ COMMENTARY

Fabry disease is a multisystem disorder resulting from intracellular accumulation of the substrate globotriaosylceramide due to α-galactosidase A enzyme deficiency. Generally presenting in male children, symptoms may not be recognized until later in life. Symptoms most commonly include painful neuropathy (72%) and angiokeratoma (88%), but cardiac involvement, cerebrovascular disease, nephropathy ranging from proteinuria to renal failure, sensorineural hearing loss, and paroxysmal vertigo are also observed. Prior to enzyme replacement therapy and kidney transplant, death occurred in the fifth decade. ■

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Peripheral Neuropathy in Systemic Amyloidosis

ABSTRACT & COMMENTARY

By Norman Latov, MD, PhD

Professor of Neurology and Neuroscience and Director of the Peripheral Neuropathy Center, Weill Medical College of Cornell University.

Dr. Latov receives grant / research support and is a retained consultant for Taleris Biotherapeutics; is a retained consultant for Novartis Pharmaceuticals and Octapharm Pharmaceuticals; and is a stockholder at Therapath LLC..

Synopsis: *Peripheral nerve involvement is common in systemic amyloidosis and may be the initial clinical manifestation.*

Source: Matsuda M, et. al. Peripheral nerve involvement in primary systemic AL amyloidosis: A clinical and electrophysiological study. *Eur J Neurol* 2010 doi:10.1111/j.1468-1331.2010.03215.x

The authors investigated the presence, clinical manifestations, and electrodiagnostic findings of peripheral neuropathy in 43 consecutive patients with primary systemic AL amyloidosis. Fifteen of the patients (35%) had neuropathic symptoms, including 11 (25.6%) with polyneuropathy, 4 (9.3%) with bilateral carpal tunnel syndrome, and 8 (18.6%) with autonomic dysfunction. The polyneuropathy was characterized by distal and symmetric impairment of all sensory modalities and early onset of painful paresthesias primarily in the legs, with autonomic involvement or orthostatic hypotension in more advanced stages. Electrodiagnostic studies revealed both motor and sensory axonal changes, including in patients without symptoms of neuropathy. Treatment consisted of high-dose melphalan with stem cell transplantation, or other chemotherapy regimens, with improvement or stabilization of the neuropathy in most patients.

■ COMMENTARY

Primary systemic amyloidosis is caused by proliferation of B-cells or plasma cells that secrete monoclonal antibodies, with deposition of amyloid fibrils derived from the immunoglobulin light chains in visceral organs and peripheral nerves. Primary amyloidosis is a progressive and potentially fatal disease, so it is important to recognize the condition and institute treatment directed at eliminating the monoclonal B-cell population and light chain deposition.

Neuropathy can be the presenting symptom of primary amyloidosis, so that the diagnosis should be considered in patients presenting with distal and symmetric axonal neuropathy, particularly if it is painful or associated with autonomic manifestations such as orthostatic hypoten-

sion, decreased sweating, urinary incontinence, sexual dysfunction, or alternating constipation and diarrhea. If other organs are involved, patients might also manifest symptoms of myopathy, congestive heart failure, or renal failure. Suspected patients can be screened by serum or urine immunofixation electrophoresis, with a monoclonal gammopathy present in approximately 90% of cases.[1] A tissue biopsy of nerve or another involved organ, demonstrating the amyloid deposits, is necessary to make the diagnosis, as a monoclonal gammopathy may not always be present, or the gammopathy can be associated with other causes for neuropathy, such as chronic inflammatory polyneuropathy, osteosclerotic myeloma, or anti-MAG or ganglioside antibodies in the absence of amyloidosis. In blind biopsies, abdominal fat pad biopsy is positive in approximately 70% of cases, but is less specific; bone marrow biopsy is positive in about 50% of cases; and rectal biopsy, including of the submucosa, is positive in approximately 80% of cases.[2]

Once amyloid deposits are identified, immunohistochemical staining is required to identify the specific light chain that is deposited, and to distinguish primary amyloidosis from secondary, or hereditary amyloidosis resulting from mutations in transthyretin, apolipoprotein A-1, or gelsolin. Familial transthyretin amyloidosis is currently treated with liver transplantation. ■

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1. Kissel JT, Mendell JR. Neuropathies associated with monoclonal gammopathies. In: *Diagnosis and Management of Peripheral Nerve Disorders*. Eds. Mendell JR, Kissel JT, Cornblath DR. Oxford, UK: Oxford University Press Inc. 2001: 272-296.
2. Kyle RA, Dyck PJ. Amyloidosis and neuropathy. In: *Peripheral Neuropathy*. Eds. Dyck PJ, et al. Philadelphia: WB Sauders. 3rd Ed. 1993: 1294-1309.

Neurological Complications of H1N1 Influenza in Children

ABSTRACT & COMMENTARY

By Sotirios Keros, MD, PhD, and Steven Weinstein, MD

Dr. Keros is Fellow, Child Neurology, Weill Cornell Medical College, New York Presbyterian Hospital; and Dr. Weinstein is Director, Pediatric Comprehensive Epilepsy Program, Weill Cornell Medical School, New York Presbyterian Hospital

Drs. Keros and Weinstein report no financial relationships relevant to this field of study.

Synopsis: *Children with H1N1 influenza are more likely to have neurologic complications compared to those with non-N1H1 seasonal influenza.*

Source: Ekstrand J, et al. Heightened neurological complications in children with pandemic H1N1 influenza. *Ann Neurol* DOI: 10.1002/ana.22184

Influenza long has been known to cause neurologic disorders, including encephalitis, encephalopathy, and seizures. Case reports of neurologic complications published during the 2009 H1N1 pandemic hinted at an increased incidence and severity of these complications when compared to previous years' non-H1N1 (seasonal) influenza A, particularly in children.

A single-center, retrospective study of children hospitalized at Primary Children's Hospital in Salt Lake City conducted by Ekstrand et al compared neurologic complications of H1N1 to seasonal influenza infections. Patients were all hospitalized, were younger than 19 years, had direct fluorescent antibody confirmed influenza A, and had new neurologic symptoms not attributable to another systemic problem. The 2009 H1N1 group was identified between April 1 and November 30, 2009, whereas the seasonal influenza group was admitted from summer 2004 to 2008. The H1N1 cases were further divided into two waves (April 1–July 31 and Aug 1–Nov 30). Qualifying neurologic disorders were seizures, including febrile seizures and status epilepticus, encephalopathy, encephalitis, headache, myositis, myalgia, aphasia, neuropathy, Guillain-Barré, and other focal neurologic signs.

In the 2004-2008 group, 234 hospitalized children were diagnosed with season influenza, with 16 meeting inclusion criteria. Of 303 children with 2009 H1N1, 18 met inclusion criteria, 9 in each wave. The H1N1 influenza group was older (mean 6.5 years vs. 2.4 years) and more likely to have an underlying medical or neurologic condition (83% vs. 25%) that included epilepsy, febrile seizures, neuromuscular disease, developmental delay, or a combination. The demographic characteristics were similar between wave 1 and wave 2.

The incidence of seizures (63% and 67%) and status epilepticus (39% and 37%) was similar between the groups. However, the H1N1 group had a statistically significant increased incidence of other neurologic symptoms including encephalopathy (n = 9), focal neurological findings (n = 5), and aphasia (n = 6).

Of those with lumbar punctures, none had CSF pleocytosis or significantly elevated protein, and one CSF sample tested for viral DNA by PCR was negative. The H1N1 group was more likely to be treated with antibiotics, antivirals, IVIG, and steroids, none with reported benefit. MRI was performed in seven children with H1N1 with three (17%) abnormal, and in five children with seasonal

influenza, all of which were normal. EEG abnormalities were present in eight of 11 patients tested in the H1N1 group, compared to one of 12 in the seasonal group. Abnormal findings included burst-suppression, diffuse slowing, and spike-and-wave discharges. Four patients had persistent neurologic deficits, of which two of three for whom follow-up was available recovered after 6 months.

There was a trend toward increased severity of illness in wave 1 vs. wave 2 of the 2009 H1N1 pandemic, with longer hospital stay, more cases of encephalopathy, focal findings, persistent neurological symptoms, and MRI and EEG abnormalities.

■ **COMMENTARY**

This is the largest study to date directly comparing the neurologic complications of the 2009 pandemic H1N1 influenza virus with non-H1N1 infections from previous years. A significant strength of the study is the large catchment area of Primary Children's Hospital that spans several states, but given the large distances to be traveled, may have led to an underestimate of complications with exclusion of milder cases not leading to hospitalization. The case ascertainment could have been alternatively skewed by the massive media coverage with multiple medical alerts for children with preexisting neurologic and other underlying medical conditions, leading to increased community awareness and hospital stays (median hospitalization stays were only 1-3 days). Although some conclusions are limited by the relatively small sample size and the retrospective design of the study, the data suggest that H1N1 infections are more likely to result in neurologic complications compared to seasonal influenza. But, are children with pre-existing neurologic conditions more likely to be infected and hospitalized with H1N1 in the first place, or of those hospitalized with influenza, is it those with neurologic and other illness who are more likely to have neurologic complications? The authors did not provide the baseline characteristics of the population of children hospitalized with influenza, and thus that question cannot be answered from the data provided.

This study emphasizes the potential severity of influenza infections in children, particularly the H1N1 subtype, and reinforces the need for vaccinations, especially in those with pre-existing medical and neurologic illness. ■

Primary Progressive Aphasia

ABSTRACT & COMMENTARY

By Cary Gunther, MD, and Michael Lin, MD

Dr. Gunther completed neurology and psychiatry residency training at New York Presbyterian Hospital / Weill Cornell Medical Center. Dr. Lin is Associate Professor of Neurology and Neuroscience, Weill Medical College, Cornell University

Drs. Gunther and Lin report no financial relationships to this field of study.

Synopsis: *Several recent studies examine the contributions of imaging, biomarkers, and neuropsychological testing to a refined understanding of the syndromes collectively known as primary progressive aphasia.*

Sources: Gunawardena D, Ash S, et al. Why are patients with progressive nonfluent aphasia nonfluent? *Neurology* 2010; 75: 588-594. Hu W, McMillan C, et al. Multimodal predictors for Alzheimer's disease in nonfluent primary progressive aphasia. *Neurology* 2010; 75: 595-602. Rohrer J, Rossor M, et al. Syndromes of nonfluent primary progressive aphasia: A clinical and neurolinguistic analysis. *Neurology* 2010; 75: 603-610.

THREE STUDIES RECENTLY PUBLISHED IN *NEUROLOGY* EXplore the complexities of primary progressive aphasia (PPA). Initially characterized by M.-Marsel Mesulam, PPA includes at least three clinical disorders in which language skills deteriorate years in advance of other significant cognitive decline. Primary nonfluent aphasia (PNFA) includes grammatical errors and loss of fluency; logopenic progressive aphasia (LPA) is characterized by halting speech; and semantic variant PPA (SV) is notable for retained fluency but impaired comprehension.

Gunawardena et al investigated the basis of nonfluent speech in PNFA. The authors asked which aspects of language dysfunction seen in PNFA could be contributing to reduced language speed. They collected speech samples and neuropsychological assessments of language and executive functioning from 16 PNFA patients and compared these to 12 individuals with behavioral variant frontotemporal dementia (bvFTD) and 13 controls. They found that executive dysfunction predicted speed of speech in bvFTD, but only measures of agrammatism predicted speed of speech in PNFA, pointing to a different underlying mechanism for slow speech. The authors also examined atrophy patterns in these patients and observed that reductions in cortical thickness in the left inferior frontal and anterior-superior temporal regions in PNFA patients correlated with slowness of speech, and overlapping areas of thinning correlated with agrammatism.

The group led by Hu et al attempted to determine the relative contributions of clinical features, formal neuropsychological evaluation, and quantitative neuroimaging to identify Alzheimer's disease as the neuropathology underlying LPA and PNFA. Working with 19 patients with each of these two clinically defined syndromes, they observed that 63% of patients with LPA and 32% of those with PNFA had CSF or autopsy results consistent with underlying Alzheimer pathology. Combining neuropsychological testing with MRI measurements of atrophy

yielded 90% specificity for CSF or autopsy diagnosis of Alzheimer pathology, while using both clinical features and neuropsychological testing resulted in 100% sensitivity. Most importantly, they determined that no single methodology was sufficient to reliably predict Alzheimer pathology or biomarkers.

In the third study, Rohrer et al sought to correlate specific features of speech seen in PPA with underlying pathophysiology. They subdivided 24 nonfluent PPA patients by presence or absence of apraxia of speech (AOS), defined as difficulty with planning and sequencing of speech sounds, and agrammatism. When both symptoms were present, parkinsonism was more likely, and the clinical syndrome most closely resembled PNFA. Cases with AOS but without agrammatism were postulated to represent a less advanced version of PNFA, though patients were not followed longitudinally. In cases with only agrammatism, three of three patients carried mutations in the progranulin gene. When neither agrammatism nor AOS was present, CSF Abeta/Tau ratios were consistent with Alzheimer pathology; moreover, these patients demonstrated episodic memory impairment. Both of the latter groups were clinically more similar to LPA.

■ COMMENTARY

A common thread in these studies is the demonstration that PPA is a heterogeneous syndrome. The rarity of PPA routinely limits the power of studies. In the Gunawardena study, liberal criteria for diagnosis were used, including some patients with features of corticobasal degeneration. Eventually, PPA patients will progress and have cognitive functions other than language affected, making recruitment of patients with isolated aphasia difficult.

The use of quantitative MRI techniques is highlighted in these studies, suggesting the need for further use and validation of neuroimaging techniques such as cerebral amyloid imaging and diffusion tensor imaging. Such approaches may shed additional light on the structural and functional compromise of brain regions in progressive language disorders. These studies also emphasize the connection between dysfunction of specific cerebral areas and neuropsychological testing results, yielding greater reliability from formal testing than from clinical phenomenology alone, even within what appears to be a well-defined clinical syndrome.

Finally, these investigations underscore the need for more autopsy data, as well as wider availability of sensitive and specific biomarkers for neurodegenerative diseases. In the study by Hu, only two patients from each group had neuropathology results available. In the work by Rohrman, although the intent was to evaluate pathophysiology, the investigators relied on biomarkers and genetic testing exclusively. Accurate surrogates for neuropathology will be even more important as disease-modifying treatments are developed. ■

Subthalamic Nucleus Stimulation and Somatosensory Temporal Discrimination in Parkinson's Disease

ABSTRACT & COMMENTARY

By Panida Piboolnurak, MD

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

Dr. Piboolnurak is on the speaker's bureau for Allergan.

Synopsis: *Although subthalamic nucleus stimulation can improve motor functions in Parkinson's disease, this study showed that it degrades somatosensory temporal discrimination possibly by modifying central somatosensory processing.*

Source: Conte, A., et al. Subthalamic nucleus stimulation and somatosensory temporal discrimination in Parkinson's disease. *Brain* 2010:133;2656-2663.

Although there are many studies on the effects of subthalamic nucleus deep brain stimulation (STN DBS) on motor functions in Parkinson's disease (PD), there are a few studies investigating the effects of STN DBS on the sensory system. This study tested the effects of STN DBS on somatosensory temporal discrimination (STD) in PD.

Thirteen patients with advanced PD and 13 age-matched healthy controls were recruited. The indications for DBS were severe motor fluctuations, dyskinesias, and motor deficits. Inclusion criteria were treatment with STN DBS for at least 12 months, mini-mental state examination (MMSE) > 24, absence of clinical sensory deficits with DBS switched on, and no changes in stimulation or medications within the past 3 months. The patients were evaluated in four conditions (off-med/off-stim, off-med/on-stim, on-med/off-stim, and on-med/on-stim). The experimental conditions were randomly assigned and counterbalanced across the patients.

MMSE, attentive matrices, Raven's Progressive Matrices, Corsi's test, Rey's test, and verbal fluency test did not significantly change across conditions. STD threshold was tested in the index finger (hand), periorbital region (eye), and neck. The thresholds were higher in the pa-

tients compared to healthy subjects, with the highest STD thresholds in the hand. There was no significant correlation between the individual UPDRS scores for the hand, neck, and face with their respective STD thresholds in all experimental conditions. The thresholds were lower in the on-med state compared to the off-med state. In the on-med state, the thresholds were higher in the on-stim than in the off-stim condition. However, in the off-med state, the thresholds were not different in the off- or on-stim condition. These findings suggest that dopaminergic therapy improves STD processing whereas STN DBS degrades the process. Given that cognition and attention were not different among four conditions, worsening in STD processing in the on-stim state cannot be explained by the DBS potential effects on cognition and attention.

The study also showed that the amplitudes of the upper limb somatosensory evoked potential (SEP) parietal component were larger in the off-stim than in the on-stim condition. There was no significant correlation between the changes in SEP component amplitudes and changes in STD thresholds in on-med/on-stim and on-med/off stim states.

The authors explained that DBS might decrease SEP amplitudes by interfering with subcortical somatosensory pathways. However, given the finding that STD thresholds changed to a similar extent on both body sides in patients with unilateral as well as those with bilateral DBS, it was unlikely that DBS interfered with the nearby somatosensory pathways. The authors proposed that DBS-induced chronic STN inactivation actively elicits changes in central somatosensory processing, possibly by altering the interplay between cortical (pre-supplementary motor area and somatosensory primary areas) and subcortical neural circuits (thalamus, striatum, subthalamic nucleus, and cerebellum). Concerning the effects of dopaminergic therapy, the authors explained that dopamine might directly modulate the neural circuits for STD process.

■ COMMENTARY

STN DBS is an effective treatment for PD patients with motor fluctuations and dyskinesias. Given the findings suggestive of central somatosensory processing interference by STN DBS, further studies on the clinical implications are essential. Another finding that needs a further investigation is the increase in STD thresholds by DBS only in the on-med state. Because the thresholds remained unchanged in the off-med/on-stim condition compared to those in the off-med/off-stim condition, this indicates that DBS did not worsen STD, but rather decreased the benefit of dopaminergic therapy on STD. Future studies on an interaction between DBS and dopaminergic therapy are required to explain this finding. ■

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

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- 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.

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- 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.

CME Questions

18. Fabry disease can cause:

a. small fiber neuropathy.

b. angiokeratoma.

c. renal failure.

d. sensorineural hearing loss.

e. All the above

19. In children, H1N1 pandemic influenza has been associated with a higher prevalence of neurological consequences than seasonal influenza.

a. True

b. False

20. The following are true about primary progressive aphasia (PPA) except for:

a. PPA is a heterogeneous syndrome of multiple etiologies.

b. PPA is a non-progressive disorder.

c. PPA may evolve into Alzheimer's disease.

d. PPA may evolve into frontotemporal dementia.

21. Based on this study, which statement is incorrect?

a. STD thresholds were higher in patients with Parkinson's disease compared to healthy individuals.

b. Dopaminergic therapy reduced STD thresholds.

c. STN DBS increased STD thresholds.

d. STN DBS degrades STD processing because of its effect on cognition and attention.

22. Patients with ischemic stroke admitted to hospital on the weekend are less likely to receive thrombolytic therapy.

a. True

b. False

23. Anticoagulation therapy is indicated for patients with lupus who have antiphospholipid antibodies.

a. True

b. False

24. Cilostazol appears to be at least as effective as aspirin in preventing recurrent ischemic stroke.

a. True

b. False

Answers: 18. e, 19. a, 20. b, 21. d, 22. b, 23. b, 24. a.

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PS Form **3526**, September 1999 *(Reverse)*

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*

'Weekend Effect' and Stroke

Source: Hoh BL, et al. Effect of weekend compared with weekday stroke admission on thrombolytic use, in-hospital mortality, discharge disposition, hospital charges, and length of stay in the Nationwide Inpatient Sample Database, 2002 to 2007. *Stroke* 2010; 41:2323-2338.

A STROKE "WEEKEND EFFECT" ON MORTALITY HAS BEEN NOTed in studies reported from countries other than the United States. The authors reviewed the U.S. National Inpatient Sample database from 2002 to 2007 for all emergency room admissions with ICD-9 classifications of acute ischemic stroke, to compare weekend vs. weekday stroke admission incidence of thrombolytic use, in-hospital mortality, discharge disposition, hospital charges, and length of stay. Adjustments were made to correct for differences in age, gender, season, median income, payer source, comorbidities, hospital location, teaching status, and hospital size.

There were 599,087 emergency room admissions for ischemic stroke: 439,181 weekday admissions and 159,906 weekend admissions. Compared to weekday admissions, patients with acute ischemic stroke admitted on weekends were slightly more likely to receive to receive thrombolytics (OR = 1.114; $P = 0.003$), incur higher total hospital charges (effect ratio = 1.001; $P < 0.001$), and have slightly longer lengths of stay (effect ratio = 1.021; $P < 0.001$). There was no difference in hospital mortality or disposition at time of discharge. ■

Anticoagulation Therapy in Patients with Myelitis

Source: Karsiari CG, et. al. Acute transverse myelitis and antiphospholipid antibodies in lupus. No evidence for anticoagulation. *Eur J Neurol* 2010; doi:10.1111/j.1468-1331.2010.03208.x

CURRENT VIEWS OF THE PATHOGENESIS OF MYELITIS IN THE setting of lupus with antiphospholipid antibodies (APLA) suggests that thrombosis and spinal cord ischemia play a significant role, and anticoagulation treatment has been recommended. There are no randomized, controlled treatment trials to support this recommendation, and the authors attempted to respond by performing a systematic literature review to explore the clinical significance of APLA and the role of anticoagulation.

The authors identified in the literature 70 patients with lupus who fulfilled the Transverse Myelitis Consortium Working Group diagnostic criteria. APLA were detected in 54% of these patients, but APLA positivity did not correlate with spinal location, relapsing form of myelitis, additional neurological manifestations of lupus, or worse clinical outcome. An unfavorable outcome was predicted by the severity of paralysis and CSF abnormalities. While all patients received major immunosuppressive therapies, severe neurological impairment was found predominantly in the APLA-negative patients. Anticoagulation therapy was more frequently administered in APLA-positive patients, but any additional therapeutic benefit was not evident. Identification of APLA in patients with lupus and myelitis does not seem to be definitive in diagnosing a thrombotic or ischemic cause of the spinal cord lesion. ■

Cilostazol in Secondary Stroke Prevention

Source: Shinohara Y, et. al. Cilostazol for prevention of secondary stroke (CSPS 2): An aspirin-controlled, double-blind, randomised non-inferiority trial. *Lancet Neurol* 2010;9:959-968.

THE ANTIPLATELET DRUG, CILOSTAZOL, IS APPROVED FOR USE in the United States for treatment of peripheral arterial disease, and in an earlier study in Japan, it was demonstrated to be superior to placebo in reducing ischemic stroke recurrence. The authors performed a randomized, controlled trial comparing 100 mg of cilostazol twice daily to 81 mg of aspirin once daily in patients who had a cerebral infarction within the previous 26 weeks, to determine the rate of recurrent ischemic stroke and monitor any hemorrhagic complications.

From 2003 until 2006, 2,757 patients with ischemic stroke were enrolled in Japan, and randomly assigned to cilostazol or aspirin. Mean follow-up time was 29 months. The primary endpoint (first occurrence of any stroke) occurred at yearly rates of 2.76% in the cilostazol group and 3.71% in the aspirin group (HR = 0.753; P = 0.357). Hemorrhagic events (cerebral hemorrhage, subarachnoid hemorrhage, or any hemorrhage requiring hospital admission) occurred in fewer patients on cilostazol than on aspirin (0.77% vs. 1.78%) but there were more side effects (headache, diarrhea, palpitation, dizziness, tachycardia) with cilostazol. Cilostazol appears to be at least as good as aspirin in reducing the risk of recurrent stroke, and may be slightly better, with fewer hemorrhagic complications. ■

In Future Issues: **Critical Care Update**

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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Can vitamins stop photoaging of the skin?

Source: Zussman J, et al. Vitamins and photoaging: Do scientific data support their uses? *J Am Acad Derm* 2010;63: 507-525.

UV light is responsible for some of the skin changes associated with aging, which is known as photoaging (PHA). Expenditures in the United States for so-called "cosmeceuticals" is anticipated to reach more than $6 billion this year, although only a few components of commonly applied topical agents have any clearly demonstrated benefit.

Vitamin A derivatives, particularly the prescription retinoids such as tretinoin cream and tazarotene, are FDA-approved for aging-related fine line wrinkles, skin roughness, and mottled hyperpigmentation. OTC vitamin A derivatives have less convincing evidence, but of these, retinol should be the preferred agent according to Zussman et al.

Amelioration of PHA has been seen in several topical vitamin C trials using L-ascorbic acid; chemically related compounds (e.g., ascorbyl palmitate, ascorbyl tetraiopalmitate) provide greater vitamin C stability, but do not have sufficient clinical trial outcomes data to advocate for them.

Topical formulations of vitamin E, although widely touted for antioxidant potential, do not have data to support their use in management of PHA. Limited data on topical niacin suggest promise.

The best method to address photoaging is overall good nutrition and an appropriate combination of sunscreen and sun avoidance. ■

Once weekly exenatide vs sitagliptin or pioglitazone for type 2 diabetes

Source: Bergenstal RM, et al. Efficacy and safety of exenatide once weekly versus sitagliptin or pioglitazone as an adjunct to metformin for treatment of type 2 diabetes (DURATION-2): A randomised trial. *Lancet* 2010;376:431-439.

The incretin class of medications (exenatide, liraglutide, sitagliptin, saxagliptin) all share the favorable quality of not being associated with weight gain. Recently published data support the efficacy, tolerability, and simplicity of once-weekly exenatide. Bergenstal et al compared exenatide once weekly (EXEN-W) with sitagliptin (STG) or pioglitazone (PIO) as add-on therapy for persons with type 2 diabetes (n = 491) who had not attained goal with metformin.

At the end of 26 weeks, several outcomes favored EXEN-W. A1c on EXEN-W was 0.6% lower than STG, and 0.3% lower than PIO. Weight loss was also greatest in the EXEN-W group. Adverse effect profiles with each treatment arm were consistent with prior trials, and the discontinuation rate was similar for each group.

EXEN-W reduced systolic BP more than sitagliptin, but similarly to pioglitazone. Favorable lipid effects were seen with each treatment arm: The greatest increase in HDL was seen with pioglitazone.

As clinicians make their therapeutic choices for diabetes management, the relevance of medication impact upon CV risk factors such as BP, weight, and lipids merits our consideration. ■

Tai chi for fibromyalgia

Source: Wang C, et al. A randomized trial of tai chi for fibromyalgia. *N Engl J Med* 2010;363:743-754.

FDA-approved pharmacologic treatments for fibromyalgia (FIB) include duloxetine, milnacipran, and pregabalin. Although each of these agents has shown both statistically significant and clinically relevant impact, few patients are relieved of all problematic symptoms. Hence, additional treatment paths for FIB are sought.

Exercise has long been recognized as having a favorable impact on FIB, although it has been uncertain which type of exercise should be preferred. For a variety of reasons, some patients will not readily embrace strenuous or aerobic exercise programs, leaving a therapeutic gap in activity programs that can be relied upon to improve FIB symptoms and functionality.

Wang et al enrolled FIB patients (n = 66) into a 12-week program comparing tai chi to a stretching + wellness education component. For the physical activities, both groups participated in two 60-minute sessions per week for 12 weeks. Fibromyalgia patients were diagnosed using the American College of Rheumatology criteria.

At the conclusion of the study, Fibromyalgia Impact Questionnaire and SF-36 physical component scores were superior in the tai chi group as compared to the stretching group. Discontinuation of medications used to treat FIB was seen in both active treatment groups, with a trend favoring tai chi.

Tai chi instruction was provided by a single tai chi master to all of the subjects in that group. Generalizability — whether clinicians can anticipate similar efficacy when tai chi is taught by others — remains to be confirmed. ■

Prevalence of hearing loss in U.S. adolescents

Source: Shargorodsky J, et al. Change in prevalence of hearing loss in U.S. adolescent. *JAMA* 2010;304:772-778.

My grandmother always claimed that listening to loud rock and roll music would be the demise of my hearing … but I still don't know if she was right. In those days we used to listen to something called a record player (younger clinicians interested to see such an archaic device can readily locate one on Google), and I have always wondered whether those cars bouncing up and down at the traffic light next to me, loaded with rap music, would be determined to be similarly ototoxic, or worse. Well, if the NHANES data are correct, we still don't know.

According to this analysis of data from NHANES, the prevalence of hearing loss has increased when one compares the 1988-1994 interval with 2005-2006. Indeed, the relative risk of any hearing loss (induced by any factor) has increased by more than 30%.

Hearing loss was associated with poverty and a history of > 3 ear infections, but not exposure to persistent (> 5 hrs/week) loud noise or firearm use. In support of grandma's point of view, a recent study from Australia noted hearing loss 70% more often in teens who had used personal stereo devices.

Overall, the prevalence of any hearing loss increased from 11.1% to 14.0% over the decade studied; further elucidation of modifiable risk factors would be helpful. ■

When to initiate dialysis? Early vs late GFR threshold

Source: Cooper BA, et al. A randomized, controlled trial of early versus late initiation of dialysis. *N Engl J Med* 2010;363:609-619.

The number of individuals requiring renal replacement therapy (dialysis) continues to grow. Because dialysis is an expensive, time-intensive, and intrusive intervention, it is wise to try to refine an optimum threshold for initiation of dialysis. Intuition might suggest that earlier is better than later, but few data to support this notion are in evidence.

Cooper et al performed a study of adults (n = 828) who qualified for dialysis. Study subjects were randomized to either early (GFR = 10-15 mL/min/1.73 m^2) or late (GFR = 5-7 mL/min/1.73 m^2) dialysis. The primary outcome of the trial was all-cause mortality.

Over an 8-year interval, 828 diabetic subjects with Stage V CKD (GFR < 15 mL/min/1.73 m^2) were randomized to initiate dialysis at either the early or late GFR threshold. The mean time to dialysis initiation in the early group was 1.8 months vs 7.4 months in the late group, but this difference might be expanded further, since more than 75% of the late start group actually initiated dialysis because of symptoms before reaching a GFR of 7.

Overall mortality during 3.6 years of follow-up was not significantly different between the two groups. There does not appear to be any mortality detriment associated with delaying dialysis until GFR is 7 mL/min/1.73 m^2 or less, although many patients may require earlier dialysis due to symptoms. ■

Postoperative abdominal wall hernias: Best repair methodology

Source: Itani KM, et al. What to advise patients about hernias. *Arch Surg* 2010;145:322-328.

The literature indicates that almost one-fourth of persons who undergo abdominal surgery will subsequently incur an abdominal wall hernia. The optimum method for repairing such hernias has not been established. Itani et al performed a randomized trial of laparoscopic vs open repair of ventral incisional hernias at four Veterans Affairs hospitals (n = 162).

There was a substantial risk reduction for complications in the laparoscopic group vs the open repair group (absolute incidence = 31.5% vs 47.9%). In particular, surgical wound site infection was almost 4-fold less in the laparoscopic group. Pain scores at 1 year were less in the laparoscopic group, and return to work was quicker. The only major advantage of open surgical treatment was the incidence of major complications, primarily bowel injury (4.4% in the laparoscopic group vs 1.4% in the open surgery group). One additional advantage of open surgical repair was a trend toward lower recurrence in this group (8.2% vs 12.5%; *P* = NS).

In general, asymptomatic incisional ventral hernias do not require repair, but once they are symptomatic, laparoscopic surgery shows distinct advantages. The surgeons in this trial had not performed a high volume of laparoscopic procedures; hence, clinicians might anticipate even better outcomes as experience accrues. ■

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Dabigatran Leading Race to Replace Warfarin

In this issue: FDA Advisory Committee recommends approval of dabigatran, safety of proton pump inhibitors, effectiveness of glucosamine and chondroitin, FDA Actions.

Advisory Committee recommends approval of dabigatran

In the race to find a drug to replace warfarin, Boehringer Ingelheim may have a leg up with the impending approval of dabigatran. The Cardiovascular and Renal Drugs Advisory Committee of the FDA unanimously recommended approval of the drug in September for the prevention of stroke and systemic clots in patients with atrial fibrillation. Dabigatran is a direct thrombin inhibitor that is given in a fixed dose twice a day and does not require monitoring. It is speculated that dabigatran will replace warfarin as the preferred anticoagulant in many settings, including many patients with atrial fibrillation. The approval was based on the Randomized Evaluation of Long-Term Anticoagulation Therapy trial, which was published last December. The study of more than 18,000 patients with atrial fibrillation showed that dabigatran given at a dose of 110 mg was similar in effectiveness to warfarin in prevention of strokes and systemic embolism, but had a significantly lower rate of major hemorrhage. A higher dose of 150 mg was associated with lower rates of stroke and systemic embolism compared to warfarin and similar rates of hemorrhage (*N Engl J Med* 2009;361:1139-1151). The FDA panel recommended approval of the higher dose, but was split on recommending the 110 mg dose. There was a slightly higher rate of heart attacks with dabigatran compared to warfarin, although the reviewers did not think this was serious enough to warrant holding the drug back. Dabigatran, once approved, will be marketed as Pradaxa®. Several companies are working on their own products to fill the same niche in what has been estimated to be a $10-20 billion market. Drugs in development include Bristol-Myers Squibb's apixaban and rivaroxaban, which is being jointly developed by Bayer Healthcare and Johnson & Johnson. Both drugs are direct inhibitors of Factor Xa. ■

Safety of proton pump inhibitors

Recent studies have suggested that proton pump inhibitors (PPIs) may negate some of the benefit of clopidogrel (Plavix®) in patients with cardiovascular (CV) disease. A new study refutes these findings, and at the same time raises more questions about the safety of PPIs. In a nationwide cohort study from Denmark, all patients discharged after first-time myocardial infarction (MI) were reviewed during 2000-2006. Of the more than 56,000 patients, 16% were rehospitalized for MI or stroke or experienced CV death. Nearly 25,000 patients were discharged on clopidogrel, of which nearly 30% received a concomitant PPI. Patients who were discharged on the combination of a PPI with clopidogrel or on a PPI alone had elevated but similar rates of death or rehospitalization for MI at 30 days (hazard ratio [HR], 1.29 for the combination [95% CI, 1.17-1.42]; HR, 1.29 for PPI alone [CI, 1.21-1.37]), indicating that

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the risk of a PPI with clopidogrel was no higher than a PPI alone. The authors conclude that there seems to be no significant interaction between PPIs and clopidogrel; however, PPIs may be associated with an increased risk for adverse CV outcomes after discharge. The authors postulate that the increased CV risk from PPIs is likely caused by unmeasured confounders (*Ann Intern Med* 2010;153:378-386). As pointed out in an accompanying editorial, this study may be very confusing for clinicians who have recently received warnings regarding the combination of clopidogrel with a PPI. It further highlights the potential risks of PPIs in patients with questionable or inappropriate indications for the drugs and the need for further studies into their risks and benefits (*Ann Intern Med* 2010;153:413-415). ■

Glucosamine and chondroitin

Millions of patients take glucosamine and chondroitin on a daily basis, hoping it is a safe alternative treatment for osteoarthritis. A new study suggests that the combination is ineffective but harmless. In a meta-analysis of 10 trials and more than 3800 patients, glucosamine, chondroitin, or the combination was compared to placebo with regard to pain scores and X-ray appearance of the hip and knee joint. None of the endpoints crossed the boundary of the minimal clinical important difference (95% credible intervals). The authors conclude that compared with placebo, glucosamine, chondroitin, and the combination do not reduce joint pain or have an impact on narrowing of joint space of the hip or knee. They further state that insurers should not cover the cost of these preparations, but since there is little harm, patients may wish to continue buying and taking it (*BMJ* 2010;341:c4675). ■

FDA Actions

The FDA has announced that it will significantly restrict the use of rosiglitazone (Avandia®) to patients with type 2 diabetes who cannot control the disease on other medications. The FDA had the option of removing the drug from the market, a move that was recently taken by the European Medicines Agency; however, the agency decided to limit access at least for now. Rosiglitazone has been associated with an elevated risk of cardiovascular events.

The FDA has approved fingolimod (Gilenya®), the first oral drug to reduce relapses and delay disability progression in patients with relapsing-remitting multiple sclerosis. The drug is the first of a new class called sphingosine 1 phosphate receptor modulators. Patients need to be closely monitored for symptomatic bradycardia. Fingolimod will be marketed by Novartis Pharmaceuticals.

The Endocrinologic and Metabolic Drugs Advisory Committee of the FDA has voted against recommending approval of lorcaserin hydrochloride for the treatment of obesity (see September *Pharmacology Watch*). Although the drug was shown to be effective, resulting in at least a 5% body weight loss for half of patients taking the drug over 1 year, there were concerns over valvular heart disease. Arena Pharmaceuticals argued that valvulopathy was not a significant issue and that they met the FDA's predefined goals for safety. The FDA is not required to follow subcommittee recommendations, however it usually does.

The same subcommittee also recently reviewed the weight-loss drug sibutramine (Meridia-Abbott Laboratories) and delivered a **split vote on whether sibutramine should stay on the market.** Sibutramine has been the subject of controversy since last November when initial data from the Sibutramine Cardiovascular Outcomes trial revealed a higher rate of cardiovascular disease associated with the drug. The full study was published in September and showed that cardiovascular events were observed significantly more frequently in the sibutramine group than in the placebo group (11.4% vs 10.0%; $P = 0.02$). The rate of cardiovascular death or death from any cause, however, was no different in the two groups (*N Engl J Med* 2010;363:905-917). The FDA subcommittee voted 8-8, with 8 members voting to remove the drug from the market and the other 8 voting to allow the drug to remain on the market with tougher warnings and a restricted distribution pattern. The FDA vote is expected later this fall.

The **FDA has approved pegloticase for the treatment of refractory gout in patients who have not responded to or can't tolerate conventional therapy.** The drug is administered intravenously every 2 weeks. It appears to work by metabolizing uric acid to allantoin, which is then cleared through the kidneys. The approval was based on two 6-month trials in more than 200 patients that showed the drug reduces uric acid levels and reduces uric acid deposits in joints and soft tissue. About one in four patients will experience severe allergic reactions to the infusion, so patients should be given an antihistamine and a corticosteroid prior to administration. The drug was not studied in patients with congestive heart failure and should not be used in this population. Savient Pharmaceuticals will market pegloticase as Krystexxa™. ■