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INSIDE

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Parkinson's Disease Genetics: New Thinking about PINK1

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

Assistant Professor, Neurology and Neuroscience, Weill Cornell Medical College

Dr. Nirenberg reports that she has consulted for Biovail.

Synopsis: *A mutation in a single copy of the PINK1 gene may be a susceptibility factor for subtle but progressive motor and non-motor signs of Parkinson's disease.*

Source: Eggers C, et al. Progression of subtle motor signs in PINK1 mutation carriers with mild dopaminergic deficit. *Arch Neurol* 2010;74:1798-1805.

Mutations in the PTEN-induced putative kinase 1 (PINK 1) gene are the second most common cause of autosomal recessive, early-onset Parkinson's disease (PD). Patients with homozygous PINK1 mutations nearly always develop PD. Little is known, however, about whether heterozygous PINK1 mutations may also cause progressive signs and symptoms of parkinsonism.

In this study, the authors performed a longitudinal analysis of four homozygous PINK1 mutation carriers (all with clinically definite PD) and 10 asymptomatic heterozygous PINK1 mutation carriers (five unaffected; five with examination findings consistent with possible or probable PD) in a single German kindred, to test the hypothesis that there is a progressive phenotype that occurs in carriers of heterozygous PINK1 mutations. All study subjects were evaluated at baseline and three years later. Baseline assessments included a videotaped Unified Parkinson's Disease Rating Scale (UPDRS) motor examination, and smell and color discrimination tasks. After three years, most of the study subjects also completed fluorodopa positron emission tomography (FDOPA PET) scans. Heterozygous PINK1 mutation carriers were compared with both homozygous PINK1 mutation carriers and healthy control subjects.

Over the three-year study period, three of the five previously unaffected heterozygous PINK1 mutation carriers had developed new signs of possible PD. At the follow-up visit, seven heterozygous PINK1 mutation carriers had hyposmia, and four had diminished color discrimination. Hyposmia, but not impairment of color discrimination, was significantly more common in

Weill Cornell Medical College

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PINK1 mutation heterozygotes than in control subjects. PET scans at the follow-up visit showed a 20% autumnal FDOPA uptake reduction in heterozygous PINK1 mutation carriers compared with healthy controls; this was a significant difference, but mild in comparison with the 60% FDOPA uptake reduction seen in subjects with homozygous PINK1 mutations. Overall, the degree of FDOPA uptake reduction correlated with severity of UPDRS motor impairment. Together, the findings suggest that heterozygous PINK1 mutations may increase susceptibility to hyposmia and motor signs of PD, but to a lesser degree than homozygous PINK1 mutations.

■ COMMENTARY

In recent years, there has been a growing recognition of the importance of genetic susceptibility factors in both familial and sporadic PD. In particular, there has been increasing evidence that heterozygous mutations in "recessive" genes for PD – including PINK1 and Parkinson's – may also confer vulnerability to PD. In this study, the authors performed a longitudinal study of a single, large kindred, and demonstrate that the mild parkinsonian signs seen in PINK1 heterozygotes are progressive over time and associated with mild but significant reduction in FDOPA uptake, thereby providing further support for this hypothesis.

The major limitation of the study is that it was restricted to a small number of subjects in a single kindred, and therefore may not be generalizable to other individuals with PINK1 mutations. In addition, the study duration was only three years, and FDOPA PET scans were only completed at the study endpoint; thus, it is not known whether the reduction in FDOPA uptake observed in subjects with heterozygous PINK1 mutations was progressive over time. Further follow-up of this and other kindreds with PINK1 mutations is therefore warranted.

While PINK1 mutations are relatively uncommon in PD, this and other genetic susceptibility factors for PD provide a unique opportunity to study the presymptomatic and premotor phases of Parkinson's disease, and to clarify the patterns of evolution of PD non-motor and motor disease progression. Such an understanding may help to facilitate the early diagnosis of both genetic and sporadic PD, and thus permit the administration of future disease-modifying therapies as early as possible in the disease course. ■

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Cholinergic Deficits Link Dementia and Olfactory Dysfunction in Parkinson's

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

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

Dr. Henchcliffe serves on the speaker's bureau of GlaxoSmithKline, Teva Neuroscience, Boehringer Ingelheim, Novartis, and Allergan.

Synopsis: *Olfactory dysfunction is associated with cognitive impairment in Parkinson's disease (PD), and both are linked by cholinergic pathway deficits.*

Source: Bohnen N, et al. Olfactory dysfunction, central cholinergic integrity and cognitive impairment in Parkinson's disease. *Brain* 2010;133: 1747-1754.

THIS STUDY EXAMINES THE RELATIONSHIP OF TWO COMMON non-motor features of Parkinson's disease (PD) that traditionally are thought to begin early (olfactory dysfunction) or late (cognitive impairment) in the disease process. Subjects with PD (n = 58) were evaluated using tests of odor discrimination (University of Pennsylvania Smell Identification Test, UPSIT), and cognitive performance (verbal and non-verbal memory, executive function and reasoning), along with age-matched healthy controls (n = 26). All subjects underwent brain nuclear imaging with the following ligands: [^{11}C]methyl-4-piperidinyl propionate to measure acetylcholinesterase (AChE) activity, reflecting cholinergic innervation; and (+)-[^{11}C]dihydrotetrabenazine, a ligand for the vesicular monoamine trans-

porter type 2 (VMAT2) protein, reflecting dopaminergic nigrostrostriatal neuron integrity. All PD patients were studied after overnight withholding of dopaminergic medications. PD subjects comprised 49 men and nine women, with mean age 69.0 ± 7.6 (range 51-83) years, and mean disease duration of 7.0 ± 3.8 years. Anticholinergic and cholinesterase inhibitor drugs were not allowed, and all subjects had a Mini-Mental State Examination score of 25 or above. UPSIT and cognitive test scores were lower in PD patients versus controls. AChE activity was reduced in PD versus controls in the hippocampus, amygdala, and neocortex, and VMAT binding was, as expected, lower in PD. In PD, UPSIT scores correlated with AChE activity in the hippocampus ($r = 0.56$, $p < 0.0001$) and amygdala ($r = 0.50$, $p < 0.0001$), independent of motor severity, disease duration, and age. Moreover, UPSIT scores were associated with higher composite memory scores ($r = 0.26$, $p < 0.05$). A post hoc analysis of milder (Hoehn and Yahr stage ≤ 2, n = 14) versus more advanced (Hoehn and Yahr stage ≥ 2.5, n = 44) PD subjects revealed a significant association of UPSIT scores with AChE activity and VMAT2 binding in milder PD, but only AChE activity, and not VMAT2 binding, in more advanced PD.

■ **COMMENTARY**

Olfactory dysfunction is strongly associated with Parkinson's disease. It may occur years before motor symptoms, and is being investigated as a possible means of identifying "at risk" individuals for further screening. The Braak hypothesis identifies α-synuclein pathology in the olfactory bulb and anterior olfactory nucleus in initial stages of PD. However, other areas likely contribute to olfactory dysfunction, and this study is an important step in dissecting the role of the limbic system and neocortex in both earlier and later stages of PD. Examining cholinergic activity in PD is interesting for a number of reasons. Loss of cholinergic innervation has been linked to cognitive dysfunction, not only in PD, but also in Alzheimer's disease and other disorders. Moreover, rivastigmine, an acetylcholinesterase inhibitor, is indicated for PD dementia treatment, and another such inhibitor, donepezil, was found in one human Alzheimer's disease study to improve odor identification. In this study, the authors not only demonstrate an association between olfactory dysfunction and a composite cognitive score, but also provide a plausible neurophysiologic explanation through a common neurotransmitter, acetylcholine. What is the practical implication of this work? Cognitive decline and dementia are unfortunately common in PD, and dementia is an independent risk factor for nursing home placement. Dementia remains poorly understood, and difficult to treat. We have as yet no way to predict the degree of risk for an individual at the time of PD diagnosis, and therefore counseling about this important and distressing possibility is limited. One hope is that olfactory testing possibly coupled with specific nuclear imaging might help stratify risk for dementia in PD, and these authors' results provide a strong platform for testing in longitudinal studies. ■

Prediabetes and Bell's Palsy

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Medical College, Cornell University

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

Synopsis: *When compared with controls, patients with Bell's palsy were found to have a higher incidence of impaired glucose tolerance.*

Source: Bosco D, et al. Bell's Palsy: A manifestation of prediabetes? *Acta Neurol Scand* 2010;June 9 [epub ahead of print].

Bell's palsy is the most common cause of peripheral facial weakness. Other causes include trauma, Lyme disease, Ramsay-Hunt syndrome, neoplasms, sarcoidosis and vasculitis. Bell's palsy has been described in all age groups, with peak incidence noted in the fifth decade of life. It occurs more commonly in diabetic patients and pregnant women. Prediabetes is defined as impaired fasting glucose or impaired glucose tolerance following a two-hour oral glucose tolerance test (OGTT). Recently, studies have demonstrated that impaired glucose tolerance is associated with peripheral neuropathy, and may be a cause in a significant percentage of patients with idiopathic peripheral neuropathy. The authors designed a prospective study to evaluate the incidence of prediabetes in patients with Bell's palsy and a control group.

Patients were included in the study if they presented with Bell's palsy. Exclusion criteria included positive family history of facial palsy, concomitant peripheral neuropathy, alcoholism, premorbid use of steroids, pregnancy, sarcoidosis, Lyme disease, autoimmune diseases, abnormal organ function, and multiple sclerosis. All patients underwent MRI, MRA, electromyography and nerve conduction studies, and chest x-ray. Blood testing was performed for ACE level, HIV, B12 deficiency, and Lyme disease. The authors reported that all of the above tests were normal in every subject. Testing for "prediabetes" included BMI, hemoglobin A1C, and glucose and insulin levels while fasting and two hours after a glucose load. Impaired glucose tolerance was defined as two-hour post-prandial glucose level between 140 and 200 mg/dL.

Diabetes was defined as fasting glucose > 126 mg/dL or two-hour glucose level > 200 mg/dL. Of note, this testing was all done before any steroid administration to treat the Bell's palsy.

The study enrolled 148 patients with Bell's palsy (mean age 56.1 years) and 128 controls (mean age 50.5 years). The mean fasting glucose was not significantly different between the two groups. However, a statistically significant difference was detected between the two groups in the results of the two-hour OGTT. In the control group, 24% demonstrated impaired glucose tolerance or diabetes (23 IGT, 8 DM). In the Bell's palsy group, 61% of patients demonstrated impaired glucose tolerance or diabetes (60 IGT, 31 DM). After adjustment for age, the differences between the groups was significant, with $P < 0.001$. Of note, waist circumference, hemoglobin A1C, mean blood pressures, lipids, and triglyceride levels were not different between the groups. The authors conclude that impaired glucose tolerance is frequently associated with Bell's palsy.

■ COMMENTARY

Most physicians in clinical practice are quite familiar with the various neurological manifestations of diabetes. Diabetes is the most common cause of peripheral neuropathy, and recent studies have shown that insulin resistance and impaired glucose tolerance contribute to the development of peripheral neuropathy. It is therefore logical to conclude that Bell's palsy, which is a mononeuropathy, would be associated with prediabetes. This study did demonstrate an alarmingly high rate of impaired glucose tolerance and frank diabetes in patients with Bell's palsy. Of note, the hemoglobin A1C and fasting glucose tests were not different between the groups. Based on the conclusions of this study, it is reasonable to consider a 2-hour OGTT in the evaluation of patients with Bell's palsy, but the results of this study should be replicated before OGTT in patients with Bell's palsy is recommended as part of routine clinical practice.

Does Surgery Influence Mortality in Refractory Partial Epilepsy?

ABSTRACT AND COMMENTARY:

By Padmaja Kandula, MD

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

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

Synopsis: *Successful surgical resection of an epileptic focus appears to reduce the long-term mortality by reducing the probability of severe epilepsy.*

Source: Bell GS, et al. Premature mortality in refractory partial epilepsy: does surgical treatment make a difference? *J Neurol Neurosurg Psychiatry* 2010;81:716-718.

THE DECISION TO UNDERGO SURGERY FOR REFRACTORY epilepsy often involves discussion of immediate operative risks such as infection, bleeding, and injury to eloquent areas of cortex. However, risk of premature mortality may not be emphasized. The authors in this study tried to answer the question: "Does surgery in medically refractory patients influence mortality?"

In this single institution, prospective study, both medical and surgical cohorts were followed from the time of initial presurgical evaluation or surgery, until the time of death or date last known to be alive. Surgical patients were assigned to six groups. Groups 1 and 2 had no seizures, or only simple partial seizures (auras). Groups 3-6 had increasingly more frequent seizures.

In the 641 nonsurgical patients, 40 deaths occurred. A little over half the deaths were attributable to SUDEP (sudden unexplained death in epilepsy). One death was due to drowning, and another was due to status epilepticus. SUDEP, drowning, and status epilepticus were classified as epilepsy-related deaths.

The maximum duration of follow up was 15.4 years. In the 561 surgical patients, 19 deaths occurred. Two patient deaths were due to SUDEP in the surgical group. The maximum follow-up for the surgical group was 17.4 years.

Of the patients in the surgical cohort at post operative year one, four deaths occurred in groups 1 and 2 (no seizures or simple partial seizures only). Nine deaths occurred in groups 3-6.

Non-operated patients were nearly 2.5 times as likely to die during follow up as those who had surgery and were 4.5 times more likely to die from an epilepsy-related cause. Surgical patients in group 3-6 were four times as likely to die as those in group 1 or 2.

■ COMMENTARY

The decision to undertake resective surgery for refractory epilepsy is a difficult decision for both patients and their doctors. Several factors, such as seizure-freedom rate, quality of life, mortality, and morbidity are important considerations in long term care planning.

Previous studies, such as the landmark Wiebe paper[1] also showed seizure-freedom rate was statistically significant (58%) for the surgically treated temporal lobe

epilepsy group versus 8% for the medically treated group. Again, in the Wiebe[1] study, the sole death in the 40 patients randomized to medical treatment was due to presumed SUDEP. No deaths were noted in the 40 patients randomized to surgery.

The authors of this study found that successful epilepsy surgery, as defined by no seizures or only simple partial seizures at follow up, was associated with decreased mortality as compared to the non-surgical cohort. However, a strong limitation of the study is the failure to address the intrinsic differences in epilepsy syndromes that may influence mortality. Further stratification of patients in both the medical and surgical cohorts according to cortical region of onset and mesial versus neocortical onset in the case of temporal lobe epilepsy, may have yielded slightly different results. In addition, there was no mention of the relative contribution of underlying pathology. A follow-up study addressing differences in epilepsy syndromes, and whether early versus late surgical intervention influences mortality is an area of further study that is needed.

Reference

1. Wiebe S, et al. A randomized, controlled trial of surgery for temporal lobe epilepsy. *N Engl J Med* 2001;345: 311-318.

Revised Electrophysiological Criteria for Diagnosis of ALS

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: *Inclusion of fasciculation potentials as evidence for denervation, will dramatically increase the diagnostic sensitivity of EMG in patients with motor neuron disease.*

Source: Douglass CP, et al. An evaluation of neurophysiological criteria used in the diagnosis of motor neuron disease. *J Neurol Neurosurg Psychiatry* 2010;81:646-649. doi: 10.1136/jnnp.2009.197434.

Electrodiagnostic confirmation of amyotrophic lateral sclerosis (ALS), based on El Escorial criteria established in 1994, revised in 1998, and currently the most commonly used in clinical studies and therapeutic trials, requires that lower motor neuron electromyographic (EMG) abnormalities in the form of positive sharp waves or fibrillation potentials be found in at least two muscles of three limbs, or two limbs and thoracic paraspinal or cranial innervated muscles, and that the two abnormal muscles be innervated by different nerve roots and different peripheral nerves. Fasciculation potentials are not accepted as evidence of denervation. Studies have demonstrated that, when patients' records are examined, El Escorial criteria remain a poor diagnostic indicator and entry into clinical trials is consequently delayed (*Neuroepidemiology* 2002:21:265-70). Might new criteria allow earlier diagnosis of ALS?

Awaji-shima, Japan, was the setting for an international symposium in 2006 where revised criteria were proposed to enhance ALS diagnostic sensitivity, including considering a limb abnormal based on either clinical or electrodiagnostic abnormalities, and considering unstable, complex fasciculation potentials equivalent to positive sharp waves as evidence of denervation. Among 205 consecutive suspected motor neuron disease (MND) patients seen at the Royal Hallamshire Hospital, Sheffield, UK,

and retrospectively reviewed, EL Escorial criteria were compared to these new proposals with respect to their sensitivity and specificity.

Motor neuron disease was the working diagnosis in 107, with neuropathy (n = 22), radiculopathy (n = 19), benign fasciculation syndrome (n = 6), and no specific disease (n = 51) making up the remaining patients. Mean age of MND patients was 64.3 years, mean duration from symptom onset to presentation was 17.9 months, and male to female ratio was 3:1. Using revised El Escorial clinical and EMG criteria, and considering all 205 patients, 21 and 12 patients were diagnosed with probable and definite MND, respectively, totaling 34 patients deemed MND positive. One hundred and one (101) patients were diagnosed with possible MND and 70 patients had no definite diagnosis. These latter two groups, encompassing 171 patients, were deemed to be MND negative. Using Awaji-shima criteria, 54 and 15 patients were diagnosed with probable and definite MND, respectively, totaling 69 patients deemed MND positive, while 67 were diagnosed with possible MND and 69 with no definite diagnosis, encompassing 136 patients deemed to be MND negative. Awaji-shima criteria would have doubled the number of patients eligible for ALS therapeutic trials, with a sensitivity of 60.7% for MND, vs. 28% for the revised El Escorial criteria. Both had a specificity of 95.9% with no difference in false positive rate. Awaji-shima criteria, accepting fasciculation potentials as evidence of denervation, allow earlier MND diagnosis and increases diagnostic certainty.

■ COMMENTARY

During needle electromyographic (EMG) study, how long must the electrode be left intramuscularly to reliably conclude that no fasciculation potentials are present? To answer this question, a small prospective study was undertaken (Mills KR. *J Neurol Neurosurg Psychiatry* 2010;doi:10.1136/jnnp.2009.186833). Among 19 patients with definite amyotrophic lateral sclerosis based on El Escorial criteria, 53 muscles were examined using a concentric needle, including the biceps (n = 8), tibialis anterior (n = 27), first dorsal interosseous (n = 17), and trapezius (n = 1). Recordings were obtained for up to 776.8 seconds with the longest inter-fasciculation interval found to be 92.2 seconds, suggesting that observation for up to 90 seconds may be necessary to reliably exclude the presence of fasciculation potentials in ALS patients. ■

CME Questions

62. Which of the following statements is true about PINK1 gene mutations?

a. Heterozygous mutations are always asymptomatic.

b. Homozygous mutations nearly always cause early-onset Parkinson's disease.

c. They are the most common cause of autosomal recessive Parkinson's disease.

d. They are the most common cause of autosomal dominant Parkinson's disease.

63. Which of the following is true about olfactory dysfunction in Parkinson's disease (PD)?

a. Olfactory dysfunction is a late non-motor feature of PD.

b. Olfactory dysfunction occurs exclusively as a result of loss of neurons in the olfactory bulb.

c. Olfactory dysfunction is associated with impaired performance on cognitive testing and with cholinergic deficits.

d. Dopaminergic deficit has no correlation with olfactory dysfunction.

e. Olfactory dysfunction occurs exclusively in individuals with PD dementia.

64. All of the following are causes of peripheral facial weakness *except* for:

a. Diabetes

b. Lyme disease

CME Objectives

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

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

CME Instructions

- 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.

c. Sarcoidosis

d. Multiple sclerosis

e. Schwannoma

65. Surgical resection for refractory epilepsy results in an increased risk of premature death.

a. True

b. False

66. During a needle electromyographic (EMG) study, how long should the needle electrode be left intramuscularly to reliably conclude that no fasciculation potentials are present?

a. 30 seconds

b. 60 seconds

c. 90 seconds

d. 120 seconds

e. 150 seconds

67. Recombinant Factor VIIa treatment does not increase the risk of thromboembolic complications.

a. True

b. False

68. Microbleeds observed on brain MRI scans may predict a worse outcome after ischemic stroke.

a. True

b. False

69. Transcranial Doppler assessment of embolic signals and intracranial stenoses may identify patients at high risk for recurrent stroke and TIA.

a. True

b. False

Answers: 62. b, 63. c, 64. d, 65. b, 66. c, 67. b, 68. a, 69. 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*

Risk of Thromboembolism in Patients Treated with Recombinant Factor VIIa for Warfarin-Associated Hemorrhages of the Central Nervous System

Source: Robinson MT, et al. *Stroke* 2010;41:1459-1463.

Intracerebral hemorrhage (ICH) associated with oral anticoagulation is a growing problem as the prevalence of atrial fibrillation increases in the aging population. The outcomes are poor due to increasing hematoma size in the first several hours, and anticoagulation should be reversed quickly. Anticoagulation is also associated with other forms of intracranial hemorrhage (subdural, epidural, and subarachnoid) that can result in catastrophic outcomes and require emergency neurosurgical intervention. In these situations, immediate reversal of anticoagulation is critical. The traditional therapy to reverse warfarin anticoagulation is the combination of fresh-frozen plasma (FFP) and vitamin K, but this protocol is slow and benefit is delayed. Recombinant Factor VIIa (rFVIIa) is a rapidly acting hemostatic agent that lowers the INR and reduces hematoma growth. The major complication of this therapy is thrombosis, and mortality has been shown to be increased from acute coronary thrombosis, as well as deep vein thromboses and pulmonary embolism.

The investigators reviewed the records of all patients at the Mayo Clinic with anticoagulation-associated hemorrhages of the central nervous system who received rFVIIa. The primary end point was the frequency of new thromboembolic events, which included myocardial in-

farction, deep vein thrombosis, ischemic stroke, and pulmonary embolism. One hundred and one (101) patients were identified; 54% had ICH and 30% had subdural hematomas. Thirteen patients (12.8%) had new thromboembolic events (10 deep vein thromboses and three ischemic strokes) within 90 days after treatment with rFVIIa. Eight of these events occurred within two weeks of therapy. The risk of thromboembolism in this group of patients is clinically important and should be considered when the use of rFVIIA is considered.

Microbleeds and Active Matrix Metalloproteinase-9 (MMP-9) Are Risk Factors for Deterioration after Lacunar Stroke

Source: Koh SH, et al. *Eur J Neurology* 2010:doi:10.1111/j.1468-1331.2010.03100.x (published online).

Brain microbleeds that are seen on T2-weighted, gradient echo MR imaging are thought to represent the result of a microangiopathic process in atherosclerosis, chronic hypertension, and amyloid angiopathy. The injured vessels are more prone to blood extravasation, resulting in small, intraparenchymal hematomas that range in size from 2 mm to 5 mm, and are clinically silent. Because brain microbleeds are a marker of significant microangiopathy, their presence might be expected to adversely effect tissue survival and alter outcome after ischemic stroke. In addition, MMP-9 is an enzyme that is normally undetectable in the central nervous system, until activated by various insults, including hemorrhage and infarction. MMP-9 plays a role in the dissolution of basement membrane proteins and blood-brain-barrier breakdown and plays an important role in tissue injury after stroke.

The investigators recruited 206 patients with a first lacunar stroke diagnosed by MRI (maximum lesion diameter of 15 mm), reviewed the MRIs for the presence of brain microbleeds, and measured venous MMP-9 levels. Neurological deterioration was defined as an increase of more than two points in the NIH Stroke Scale, 14 days after stroke onset. Seventy-nine patients (38.3%) had microbleeds and 48 (23.3%) showed neurological deterioration. Active MMP-9 levels were significantly elevated among patients with microbleeds ($p < 0.001$) and the presence of microbleeds and elevated MMP-9 were independent risk factors for neurological deterioration. Assessing these indicators at time of admission may be useful in identifying patients at risk for deterioration.

Transcranial Doppler Assessment of Embolic Signals and Intracranial Stenosis May Improve Selection of Patients Who May Benefit from Carotid Endarterectomy

Sources: Markus HS, et al. *Lancet Neurol* 2010;9:663-671; Meseguer E, et al. *Ann Neurol* 2010;68:9-17; Easton JD, et al. *Ann Neurol* 2010;68:1-2.

Several recent studies have looked at the utility of using transcranial Doppler (TCD) to identify patients with transient ischemic attacks (TIA) or asymptomatic carotid artery stenosis who would most benefit from carotid endarterectomy (CEA), by measuring the frequency of microembolic signals from the stenotic artery, and assessing for intracranial stenosis.

The Asymptomatic Carotid Emboli Study (ACES) prospectively examined 467 patients with asymptomatic carotid artery stenosis of at least 70% with repeated TCD microembolism studies over a period of two years and noted the development of any ischemic stroke or TIA. Embolic signals were present in 77 of 467 patients at baseline and the hazard ratio for risk of ipsilateral stroke or TIA over two years of follow-up was 5.57 ($p < 0.007$). The absolute annual risk of stroke or TIA between baseline and 2 years for those with embolic signals was 7.13% compared to 3.04% in those without embolic signals.

In a related study, Meseguer and colleagues performed TCD studies in 1,823 patients within four hours of admission to their TIA clinic. Intracranial narrowing or occlusion (TCD criteria) was found in 8.8% of patients, and was independently associated with age, hypertension, and diabetes. After one-year follow-up on best medical therapy, the incidence of recurrent vascular events (TIA recurrence, stroke, myocardial infarction, vascular death) was 7.0% in those with intracranial narrowing of occlusion and 2.4% in those without ($p < 0.007$).

Transcranial Doppler is a rapid, safe, and cost-effective diagnostic tool to risk-stratify patients who have carotid artery stenosis and help to select those who are most likely to benefit from surgery. ■

In Future Issues: Traumatic Brain Injury

Clinical Briefs in Primary Care™

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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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Dietary added sugar and lipids

Source: Welsh JA, et al. *JAMA* 2010;303:1490-1497.

Processed foods often contain added sucrose or high-fructose corn syrup to enhance palatability. Such added sugars (aSUG) may comprise as much as 16% of Americans' caloric intake. The Institute of Medicine suggests a 25% maximum of daily calories from aSUG and the American Heart Association suggests a 5% maximum. The incidence of obesity, diabetes, and dental caries is associated with increased aSUG, but the relationship between aSUG and lipids is less well-defined.

Welsh et al studied the relationship between aSUG and lipids in NHANES participants (n = 6113). Overall, approximately 16% of calories daily were supplied by aSUG in this population of adults. Excluded from analysis were persons with dietary reports that appeared unreliable (e.g., < 600 calories/d), marked triglyceride elevation, BMI > 65 kg/m^2, and those taking cholesterol-lowering medications.

There was a statistically significant association between progressively higher levels of aSUG and lower HDL. Similarly, LDL and triglyceride levels were linearly related to aSUG, although the LDL results were not statistically significant in men.

The mechanism(s) by which aSUG consumption is related to lipid levels is incompletely understood, although it is recognized that fructose may stimulate hepatic lipid production and reduce peripheral lipid clearance. Although not demonstrated in a clinical trial, conceptually, reductions in aSUG on a population-wide basis could have important public health benefits. ■

Underrecognition of adverse effects

Source: Zimmerman M, et al. *J Clin Psychiatry* 2010;71:484-490.

The design of clinical trials sometimes allows for failed detection of adverse effects related to medication. Perhaps the most widely recognized disconnect is in relation to ACE inhibitors: Prescribing information suggests a very low incidence of cough (typically < 10%), yet clinical experience suggests twice that frequency. The primary reason for this incongruence is that most side effects are passively reported; for a variety of reasons, patients may fail to spontaneously report adversities that could be related to medication.

Zimmerman et al addressed this issue among depressed outpatients treated with a variety of antidepressants and anxiolytics. Subjects were seen by board-certified psychiatrists, and after their office visits, filled out questionnaires addressing adverse effects possibly related to medication.

Over a 6-week interval, more than 25% of the 2233 reported side effects occurred at least daily, but fortunately, the majority were rated low on the severity scale. Only about 20% of individuals rated adverse effects as 4-5 on a 5-point scale.

Overall, 20 times more adverse effects were identified by questionnaire than in psychiatrists' records. Comparison limited to either highly frequent or bothersome adverse effects still found that questionnaires identified 2-3 times as many adversities as clinicians had recorded.

A number of explanations can clarify some of this discrepancy: Psychiatrists may not record all adverse effects they see, patients may not report all issues that bother them (or minimize the bother), and some adverse effects may be so anticipated that their presence does not merit specific notice. In any case, it appears that patients shoulder a much higher level of adverse effect burden when treated for depression than would be readily apparent from review of their clinical records. ■

Female sexual dysfunction in diabetes

Source: Esposito K, et al. *Int J Impot Research* 2010;22:179-184.

Male sexual dysfunction is well recognized as a consequence of diabetes. Currently, there are no approved medications for treatment of female sexual dysfunction (FSD), though epidemiologic surveys suggest that the population prevalence of FSD rivals that of male sexual dysfunction. FSD is typically categorized as either disorders of desire, arousal, orgasm, or pain. Of course, FSD subcategories are commonly comorbid.

This study recruited adult type 2 diabetic women (mean age, 58 years) attending a clinic in Italy for routine care of diabetes to complete the Female Sexual Function Index, a validated instrument for assessing FSD.

Overall, the prevalence of FSD in the entire population was 53%. This is similar to, but even greater than, the prevalence reported in two large population surveys (both with broader age range, and not limited to diabetics), which indicated an FSD

prevalence of 43%. FSD was 30% more frequent in postmenopausal women than premenopausal women and was associated with depression. The only recognized protective factor was physical activity.

The etiology of FSD in diabetes is unclear, and may include vascular, neurologic, and endocrinologic factors. The high prevalence of FSD in diabetic women should motivate clinicians to be more proactive in its identification. ■

Vitamin D from the sun or supplements?

Source: Terushkin V, et al. *J Am Acad Dermatol* 2010;62:929.e1-9.

While I cannot speak for you, my recent experience is that under every rock I overturn is a vitamin D-deficient patient. At least that's what checking 25-OH vitamin D levels (the currently recommended test for vitamin D status) suggests. Should we recommend sun exposure, supplements, or both to address hypovitaminosis D?

Terushkin et al compared the amount of sun exposure necessary to provide the same plasma vitamin D levels as a 400 IU/d vitamin D supplement. They chose to study individuals in Miami, FL, and Boston, MA. Of course, sun exposure varies depending upon geography and season, as well as skin type. In July, the amount of sun time to provide as much systemic vitamin D as 400 IU orally was the same in both cities (3 min at 12 noon). A darker-skinned individual would require 5 min.

During winter months, there were marked differences in required exposure time. In Miami, 6 min of sun vs 23 min of sun in Boston would be required. Since most individuals do not expose 25% of the body surface (the face is only 3.5%) to sun during the winter in cities like Boston, a correspondingly greater time exposure would be required … an unlikely scenario.

Because of the concern about sun exposure and its relationship to photoaging and skin cancer, as well as the neglect of optimum sunscreen utilization, the authors of this article favor vitamin D supplementation over sun exposure as the safest way to maintain vitamin D adequacy. ■

Exenatide + rosiglitazone added to metformin

Source: DeFronzo RA, et al. *Diabetes Care* 2010;33:951-957.

It is widely recognized that approximately half of beta-cell function (BCF) has been lost by the time type 2 diabetes (DM2) is diagnosed. Additionally, it appears that despite vigorous treatment, loss of BCF continues inexorably.

The most recently published treatment algorithm for DM2 management by the ADA suggests that initial therapy should be lifestyle with metformin, unless a specific contraindication to metformin exists. Over time, however, most patients will require augmentation of treatment.

Exenatide (EXE) and rosiglitazone (ROS) are effective therapies for glucose control and work by complementary mechanisms of action. Additionally, sometimes thiazolidinedione therapy is compromised by weight gain, but since exenatide consistently provides weight loss, their combination is clinically sensible.

DM2 subjects already on treatment with lifestyle plus metformin (n = 101) were randomly assigned to add-on therapy with EXE alone, ROS alone, or EXE + ROS, and followed for 20 weeks. BCF was measured by the glucose disposition index.

In addition to the anticipated reduction in A1c by polypharmacy, EXE + ROS provided significant improvements in insulin secretion and overall BCF. Long-term studies are necessary to discern whether these favorable effects can be sustained and translated into risk reduction for macro- and/or microvascular outcomes. ■

Intensive BP control in diabetes

Source: Accord Study Group. *N Engl J Med* 2010;362:1575-1585.

Because it is recognized that type 2 diabetics (DM2) incur greater risk of CV outcomes than the general population, consensus groups have advocated BP < 130/80 mmHg as a preferred goal, in contrast to 140/90 mmHg for the general hypertensive population. Despite enthusiasm for this posture, and essentially global advocacy for the concept that lower is better in diabetes, no prospective, randomized trial has been done that confirms such benefits. The ACCORD trial was designed to compare CV outcomes achieved with tight BP control (SBP < 120 mmHg) vs standard therapy (SBP < 140 mmHg). The ACCORD trial had several limbs, including a glucose control and a lipid control arm, which were not addressed in this publication.

Almost 5000 diabetics were randomly assigned to intensive BP vs standard BP treatment and followed for the primary endpoint of (composite) nonfatal MI and stroke, or CV death over a mean 4.7-year follow-up.

The tight control arm managed to achieve an SBP of 119.3 mmHg, compared to the standard treatment group SBP of 133.5 mmHg; of course, the number of medications required to attain control was substantially greater in the tight control group (3.4 drugs vs 2.3 drugs). Intensive BP lowering did not reduce the primary endpoint. Intensive BP control was associated with more adverse events.

No hypertension guidelines have been issued since the publication and promulgation of the ACCORD BP trial. Expert opinions vary in interpretation of this outcome. I have suggested that, in the absence of proven benefit by greater BP lowering, achievement of < 140/90 mmHg now represents a reasonable goal until further literature suggests otherwise. ■

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Aggressive Modification of Cardiovascular Risk Factors

In this issue: Aggressive approach to CVD reduces MI, folic acid and vitamin B12 for CAD, corticosteroids for acute exacerbations of COPD, prescription drug abuse among young adults, and ARBs and cancer risk.

CVD decreases with aggressive treatment

Aggressive modification of cardiovascular risk factors seems to be paying dividends, at least for a large population of insured patients in Northern California. In an analysis of nearly 18.7 million patient-years between 1999 and 2008, the rate of myocardial infarction (MI) increased in 1999 and 2000 and then decreased significantly every year thereafter (287 cases/100,000 person-years in 2000, decreasing to 208 cases/100,000 person-years in 2008; 24% relative decrease over the study period). The rate of ST-segment elevation MI decreased over the study period (133 cases/100,000 person-years in 1999 to 50 cases/100,000 person-years in 2008; $P < 0.001$) and the 30-day mortality rate decreased from 1999 to 2008 as well (adjusted odds ratio, 0.76; 95% confidence interval, 0.65-0.89). This occurred despite more aggressive diagnosis of MI.

The authors conclude, "The lower incidence of myocardial infarction — particularly ST-segment elevation myocardial infarction — is probably explained, at least in part, by substantial improvements in primary-prevention efforts, …" including statins and aggressive blood pressure reduction, as well as use of cardioprotective medications such as aspirin (*N Engl J Med* 2010;362:2155-2165).

An accompanying editorial points out that while these trends are generally the case in the United States, there are significant geographic differences. "The risk among residents of Oklahoma, the lower Mississippi corridor, and Appalachia, for example, is double that among other Americans, … " suggesting socioeconomic factors play a role. Hypertension and diabetes rates have increased slightly over the last decade, while smoking rates have decreased. Perhaps even more importantly, statin use has increased significantly (among those between age 45 and 64 years, statin use in men increased from 2.5% to 16.8% and from 1.9% to 13.5% in women; among those 65 years of age or older, statin use increased from 1.9% to 38.9% in men and from 3.5% to 32.8% in women). Aspirin, beta-blockers, and ACEIs/ARBs have also contributed to the decline in cardiovascular mortality in the United States (*N Engl J Med* 2010;362:2150-2153). ■

Folic acid and vitamin B12 for CAD

Unfortunately, lowering homocysteine with folic acid and vitamin B12 does not seem to be a benefit to patients with coronary artery disease. In a study from the United Kingdom, more than 12,000 survivors of myocardial infarction were randomized to 2 mg folic acid plus 1 mg vitamin B12 daily vs matching placebo, with the main outcomes being first major vascular event such as coronary event, stroke, or noncoronary revascularization. Folate and vitamin B12 were effective at reducing homocysteine levels by 28%; however, there was no difference in the rate of major vascular events over the 6.7 years of follow-up (25.5% active treatment vs 24.8% placebo; $P = 0.28$). Individually, there was no effect on major coronary events, stroke, or noncoronary

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revascularizations, nor was there a survival benefit from active treatment. Interestingly, the authors also looked at incidence of cancer and found no difference in that outcome either. The authors conclude that long-term reductions in blood homocysteine levels with folic acid and vitamin B12 do not have a beneficial effect on vascular or cancer outcomes (*JAMA* 2010;303:2486-2494). ■

Corticosteroids for exacerbations of COPD

Giving corticosteroids orally in lower doses is as effective as giving the drugs intravenously at higher doses for the treatment of acute exacerbation of COPD (ae-COPD), according to a recent study in the *Journal of the American Medical Association*. The records of nearly 80,000 patients in more than 400 hospital admissions for ae-COPD who received steroids were reviewed. The primary outcomes were treatment failure, defined as the initiation of mechanical ventilation, inpatient mortality, or readmission within 30 days. The vast majority of patients (92%) received IV steroids. After multivariate adjustment, the death rate was similar in the two groups (1.4% IV therapy vs 1.0% oral) and the composite outcome was also similar (10.9% IV vs 10.3% oral). In a propensity-matched analysis, the risk of treatment failure was actually significantly lower among orally treated patients (odds ratio, 0.84; 95% confidence interval, 0.74-0.95), as was the length of stay and cost. Of the orally treated patients, 22% were switched to IV therapy later in the hospitalization.

The authors conclude that for patients admitted for ae-COPD, low-dose steroids administered orally are as effective, and may be safer, than higher-dose IV steroids (*JAMA* 2010;303:2359-2367). An accompanying editorial suggests that rather than doing large non-inferiority studies to confirm these findings, sufficient evidence exists to change practice now with continued comparative effectiveness research via linked registries (*JAMA* 2010;303:2409-2410). ■

Prescription drug abuse in young adults

Prescription drugs are the new drugs of abuse among young adults. While drug use in general seems to be dropping in high schools, prescription drug abuse is skyrocketing. The recently published National Youth Risk Behavior Survey from the Centers for Disease Control and Prevention (CDC) showed that 1 of 5 high school students in the United States reported abusing a prescription drug at some time in their lives. The most commonly mentioned drugs were OxyContin®, Percocet®, Vicodin®, Adderall®, Ritalin®, and Xanax®. Prescription drug abuse was most common among white students (23%), followed by Hispanic students (17%), and then black students (12%). Not surprisingly, high school students were most likely to abuse drugs in their senior year (*MMWR* 2010;59:1-142). While many teens get their prescription drugs from medicine cabinets of family and friends, others order them online, and recently many drug dealers have begun specializing in prescription drugs.

Many young adults, however, seek opioids and benzodiazepines from physicians, especially in emergency departments (ED). A new report from *MMWR* reports that ED visits for nonmedical use of opioid analgesics increased 111% from 2004 to 2008 and increased 29% from 2007 to 2008 alone. The highest number of ED visits was recorded for oxycodone, hydrocodone, and methadone. ED visits for benzodiazepines also increased 89% over the same period. In 2008, the rates of visits for both opioids and benzodiazepines increased sharply after age 17 and peaked in the 21-24 year age group. During the 2004-2008 study period, the largest increase in ED visits to obtain drugs occurred among persons age 21-29 years. Findings were from the CDC and the Substance Abuse and Mental Health Services Administration, reviewing data from the Drug Abuse Warning Network (*MMWR* 2010;59:705-709). ■

ARBs and cancer risk

Do angiotensin receptor blockers (ARBs) increase the risk of cancer? In a widely reported study, researchers from Case Western Reserve performed a meta-analysis of 5 trials for which cancer data were available from more than 61,000 patients. Telmisartan was the ARB used in nearly 86% of the studies. Patients randomly assigned to receive ARBs had a rate of new cancer occurrence of 7.2% vs 6.0% for placebo (relative risk [RR], 1.08; 95% confidence interval [CI], 1.01-1.15; $P = 0.016$). The risk ratio was higher when the analysis was limited to trials where cancer was the prespecified endpoint (RR, 1.11; 95% CI, 1.04-1.18; $P = 0.001$). There was no difference in the rate of cancer deaths between the two groups. The authors conclude that this trial suggests that ARBs are associated with a modestly increased risk of new cancer diagnosis, but it is not possible to draw conclusions about the exact risk of cancer associated with each particular drug and further research is warranted (*Lancet Oncology* 14 June 2010; early online publication). ARBs are involved in the regulation of cell proliferation, angiogenesis, and tumor progression, which are possible mechanisms for these findings. ■