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INSIDE

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Churg-Strauss Syndrome: A Cause of Painful Neuropathy

ABSTRACT & COMMENTARY

By John J. Caronna, MD

Professor of Clinical Neurology, Weill Cornell Medical College

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

Synopsis: *Churg-Strauss syndrome is an immune-mediated disorder that commonly affects the peripheral nervous system.*

Source: Wolf J, et. al. Neurologic complications of Churg-Strauss Syndrome – A prospective monocentric study. *Eur J. Neurol* 2009; do1: 10.111/j. 1468-1331, 2009. 02902. Finsterer J. Editorial: Neurological manifestations of Churg-Strauss Syndrome. *Eur J Neurol* 2009; do1: 10.111/j. 1468-1331, 2009. 02903

CHURG-STRAUSS SYNDROME (CSS) WAS CLASSIFIED AS A VARIANT OF POLYarteritis nodosa (PAN) until 1951.[1] Although it shares various clinical laboratory and pathological characteristics with both PAN and Wegener granulomatosis, a distinct combination of features identifies CSS as a separate entity. The distinctive features of CSS are adult onset asthma that precedes the occurrence of systemic vasculitis, and a peripheral and tissue eosinophilia. The neurologic abnormalities of CSS — mononeuritis multiplex and distal symmetric polyneuropathy — are similar to those in PAN.[2]

Wolf et al have reported a prospective study of 14 patients (7 men and 7 women) with CSS, 12 of whom presented with neurologic involvement. All the patients had a history of asthma and eosinophilia. Eosinophils were 21% to 85% of total leukocyte counts. All of the patients had severe multi-organ involvement by systemic vasculitis at the time of initial diagnosis. The mean age was 55 ± 14 years (range 34–75).

At presentation, ESR and CRP were elevated in 10 patients. Antineutrophil cytoplasmic antibodies (ANCA) were positive in four patients, with a perinuclear fluorescence pattern (p-ANCA) in three, and with a cytoplasmic pattern (c-ANCA) in one. The presence of ANCA was associated with higher values of CRP ($p < 0.01$).

All patients received a detailed neurologic examination and motor

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and sensory nerve conduction studies as well as needle EMGs. Of the 12 who presented with neurological involvement, eight had mononeuritis multiplex (sural, common and deep peroneal, posterior tibial, median, ulnar, radial, and lateral femoral cutaneous nerves), three had an axonal polyneuropathy, three had neuropathy of cranial nerves (facial palsy, anterior ischemic optic neuropathy), and two had cerebral infarcts in the basal ganglia. In one patient, muscle biopsy revealed myositis.

Severe neuropathic pain, present in eight of eleven patients with peripheral neuropathy, decreased with the initiation of immunosuppressive therapy despite the persistence of axonal neuropathy. Neurological involvement, primarily mononeuritis multiplex followed by symmetrical polyneuropathy and cranial neuropathy was frequent in CSS but the outcome was favorable if treatment was initiated early.

■ COMMENTARY

CSS is increasingly recognized but remains an uncommon disease of unknown cause. ANCA probably play an important role in the pathological mechanism of disease. Asthma is the cardinal feature of CSS and presents long before the onset of systemic vasculitis. An eosinophilia of more than 10% on differential WBC count also precedes multisystem involvement. A vasculitis of small and medium-sized arteries, if untreated, leads to death because of damage to the lungs, kidneys, heart and other organs.[1] Peripheral nervous system manifestations occur in up to 75% of patients with CSS, CNS involvement in less than 10%. In CSS, as in PAN and SLE, inflammation of central nervous system (CNS) vessels is less frequent than of visceral or peripheral nervous system arteries. CNS complications tend to occur later and are due to hypertension, vaso-occlusive changes in arteries or cardiac-origin emboli.

The study by Wolf and colleagues is a reminder that in patients with painful neuropathy and a history of asthma, sinusitis or stroke, one should consider CSS. ■

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Genetic Factors Point to Cholesterol Metabolism in Alzheimer's Disease Risk

ABSTRACT & COMMENTARY

By Michael Lin, MD

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

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

Synopsis: *Cholesterol ester transfer protein gene alleles may confer longevity as well as a reduced risk for Alzheimer's disease.*

Source: Sanders AE, et. al. Association of a functional polymorphism in the cholesteryl ester transfer protein (CETP) gene with memory decline and incidence of dementia. *JAMA* 2010 ;303(2):150-158.

THE APOLIPOPROTEIN E (apoE) GENE IS ASSOCIATED WITH risk of late-onset Alzheimer's disease (AD). The E4 allele is associated with increased AD risk, and the E2 allele with decreased AD risk. In a recent study, Sanders and colleagues examined the V405 allele (valine at codon 405 instead of isoleucine) of another gene involved in cholesterol homeostasis, the cholesteryl ester transfer protein (CETP). This allele of CETP had previously been associated with increased longevity, and the authors now show in a prospective cohort study that it is associated with decreased risk for memory decline and dementia.

CETP mediates the exchange of cholesteryl esters from high density lipoprotein (HDL) to apoB-containing lipoproteins, promoting uptake of cholesterol by the liver. The common V405 allele is associated with reduced se-

rum CETP levels and activity, increased HDL levels, and increased HDL and LDL particle sizes. These changes are associated with reduced risks for hypertension, cardiovascular disease, and the metabolic syndrome, and with exceptional longevity — V405 homozygosity is present in 25% of centenarians compared to 9% of those in their 70s.1 Moreover, in a previous cross-sectional study, V405 homozygosity appeared to protect cognitive function.[2] Centenarians with good cognitive function had a higher frequency of V405 homozygosity than those with poor cognition (29% vs 14%). In an independent cohort of subjects age 75–85, those without dementia were five times more likely to be V405 homozygous than those with dementia (21% vs 4%).

The authors now report on a 15-year, prospective, community-based study drawn from the Einstein Aging Study in the Bronx. Subjects were adults age 70 years or older, identified from lists of Medicare recipients or registered voters, who were ambulatory and non-institutionalized. From 1994 to 2009, participants had annual cognitive examinations, including tests of episodic memory (Free and Cued Selective Reminding Test, FCSRT), attention (digit span), and psychomotor speed (digit-symbol substitution). The associations of V405 genotype with longitudinal cognitive performance and with incident dementia were then examined, with adjustments for sex, race, education, apoE4 status, and medical comorbidities.

Out of 523 subjects non-demented at baseline, with available CETP genotype and adequate follow-up, 178 were I405 homozygotes, 110 were V405 homozygotes, and 235 were heterozygotes. On the FCSRT memory test, V405 homozygotes lost only 0.21 [95% CI, 0.04–0.39]) points/year compared to 0.43 [95% CI, 0.29–0.58] points/year for I405 homozygotes. Although the absolute magnitude of the difference was small (0.22 [95% CI, 0.02–0.41] points/year on a 48 point scale), it was statistically significant ($p = 0.03$). Heterozygotes were indistinguishable from I405 homozygotes. There was no difference among CETP genotypes in tests of attention (digit span) or psychomotor processing speed (digit-symbol substitution).

There were 40 cases of incident dementia during follow-up. Compared to I405 homozygotes, the hazard ratios for V405 homozygotes were 0.28 [95% CI, 0.10–0.85] ($p = 0.02$) for dementia and 0.31 [95% CI, 0.10–0.95] ($p = 0.03$) for AD. The hazard ratios for heterozygotes were also less than 1, but did not reach statistical significance.

■ COMMENTARY

This is the first longitudinal study suggesting that the longevity-associated V405 allele of CETP is associated with slower memory decline and decreased risk of dementia and AD. This observation is promising for several reasons. It accords with a previous cross-sectional study from the same group showing that this allele is associated with better cognitive status.[2] Additionally, heterozygotes have an intermediate dementia risk, suggesting a gene dose effect, adding to biologic plausibility. The association of apoE with AD risk also lends plausibility to involvement of another gene related to cholesterol homeostasis.

On the other hand, apoE is still the only genetic risk factor for AD that has held up robustly in multiple studies. One previous case-control study of V405 CETP in AD showed an elevated odds ratio (1.67) for AD in non apoE4 carriers,[3] and two recent genome-wide association studies identifying apoJ as an AD risk did not identify CETP. Thus, replication is still needed. In vitro studies establishing mechanism would also be helpful in proving a role for CETP in AD pathogenesis. If valid, then reduction in CETP levels or activity, mimicking the effect of the V405 allele, could be a potential pharmacologic target for AD prevention. ■

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Migraines in Mice Explain Human Experience in Hereditary Migraine Subtype

ABSTRACT & COMMENTARY

By Dara Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a retained consultant for Boehringer Ingelheim, Merck, and Ortho-McNeil, and is on the speaker's bureau for Boehringer Ingelheim and Merck.

Synopsis: *A knock-in mouse model of a specific variant of familial hemiplegic migraine links the clinical manifestations of this rare migraine symptom with the triggering and propagation of cortical spreading depression and other unique characteristics of migraine.*

Source: van den Maagdenberg AM, et al. High cortical spreading depression susceptibility and migraine-associated symptoms in Ca(v)2.1 S218L mice. *Ann Neurol* 2010;67:85-98.

FAMILIAL HEMIPLEGIC MIGRAINE (FHM), AN AUTOSOMAL dominant subtype of migraine associated with attacks of transient hemiparesis and other neurological aura symptoms, has been studied to elucidate the pathogenetic mechanisms of more common migraine types. Overlapping features of FHM and migraine both with and without aura validate the use of this rare migraine subtype, which has been linked to three specific genes. FHM1 is caused by mutations in the *CACNA1A* gene that encodes the pore-forming subunit of neuronal Ca(V)2.1 Ca(2+) channels. In humans, the S218L *CACNA1A* mutation variant of FHM1 causes a dramatic hemiplegic migraine syndrome that is associated with slowly progressive cerebellar ataxia, seizures, and severe, sometimes fatal, brain edema, often triggered by mild head trauma.

Animal models have been invaluable in analyzing the phenotypic, molecular, and electrophysiological consequences of human disease, and are especially applicable to migraine. Researchers from Leiden University Medical Center studied the mechanisms for the S218L syndrome using transgenic knock-in mice bearing the S218L missense mutation in the mouse *CACNA1A* gene.

The *CACNA1A* (S218L) mice, who faithfully mimicked the associated clinical features of the human S218L syndrome, were phenotypically normal between attacks except for mild cerebellar ataxia. Their poor performance on ataxia testing correlated pathologically with reduced arborization of cerebellar Purkinje neurons. These mice also had decreased life expectancy with death due to lung edema, perhaps correlated with sudden seizure-associated death, and exhibited significant brain edema after mild head impact. S218L neurons exhibited a gene dosage-dependent negative shift in voltage dependence of Ca(V)2.1 channel activation, resulting in enhanced neurotransmitter release at the neuromuscular junction. *CACNA1A* (S218L) mice also display an exquisite sensitivity to cortical spreading depression (CSD), the pathophysiological correlate of the migraine aura, with a vastly reduced triggering threshold, an increased propagation velocity, and frequently multiple CSD events after a single stimulus. This response correlates clinically with the increased sensitivity of the FHM1 S218L brain to even mild stimuli such as low-impact head trauma. The particularly low CSD threshold and the tendency to respond with multiple CSD events after a single stimulus indicate that the S218L cortex is highly vulnerable to weak stimuli and may provide a mechanistic basis for the dramatic phenotype seen in S218L mice and patients. In comparison, knock-in mice for another variant of FHM1, the R192Q CACNA1A mutation, which in humans causes a milder form of hemiplegic migraine, typically exhibited only a single CSD event after one triggering stimulus.

■ **COMMENTARY**

Migraine, in its multiple clinical manifestations, afflicts millions of Americans and, despite recent advances in its acute treatment and prevention, is associated with extraordinary disability. The S218L mouse model may prove a valuable tool to further elucidate mechanisms underlying migraine, seizures, ataxia, and trauma-triggered cerebral edema. However, the most disabling aspect of migraine for most sufferers is the severe head pain with accompanying nausea and vomiting. The mice migraineurs, who mimic a rare migraine variant, do not indicate if they experience head pain and nausea so while the mouse model is a promising first step toward understanding the pathophysiology of migraine and having a substrate on which to test new therapies, more investigation is needed before all the mysteries of migraine are revealed. An animal model is a crucial first step and the work of the researchers from the Leiden University Medical Center illustrates the important contribution of the judicious use of animal models to our understanding and treatment of human disease. ■

Deep Brain Stimulation in the Pedunculopontine Nucleus Area in Parkinson's Disease

ABSTRACT & COMMENTARY

By Panida Piboolnurak, MD

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

Dr. Piboolnurak reports no financial relationship relevant to this field of study.

Synopsis: *PPN DBS may be able to improve gait and postural stability in advanced Parkinson's disease. Although double-blind studies with small sample size did not confirm this effect, further studies are required for better understanding of the effects of PPN DBS in Parkinson's disease.*

Sources: Ferraye MU, et al. Effects of pedunculopontine nucleus area stimulation on gait disorders in Parkinson's disease. *Brain* 2010:133;205-214. Moro E, et al. Unilateral pedunculopontine stimulation improves falls in Parkinson's disease. *Brain* 2010:133;215-224.

GAIT DISTURBANCE AND POSTURAL INSTABILITY ARE MAJOR causes of disability in Parkinson's disease. Medications and deep brain stimulation (DBS) in the subthalamic nucleus or internal globus pallidus sometimes do not alleviate freezing of gait and usually do not provide a direct benefit on postural stability. Pedunculopontine nucleus

(PPN) is a reticular structure belonging to the mesencephalic reticular formation. Studies in non-human primates suggested a role of PPN and related brainstem areas in gait and posture control. Recent open-label studies also suggested that PPN DBS may provide benefit on gait disorders. Ferraye and Moro and their respective groups conducted double-blind studies on the effects of PPN DBS.

Ferraye evaluated the effects of bilateral PPN DBS in six patients with Parkinson's disease with severe gait freezing, unresponsive to levodopa and STN DBS. At one-year follow-up, during the open-label assessment, although freezing of gait improved in the off-medication / on PPN stimulation state, there was no significant change in the on-medication state compared to pre-surgery condition whether or not PPN DBS was on or off. Moreover, during the double-blind evaluation, there was no significant difference in gait freezing and motor scores between off and on stimulation states. The best stimulation contacts located slightly posterior to the PPN, in the cuneiform and subcuneiform nuclei. Bipolar stimulation was used in most patients with stimulation frequency ranging from 15 to 25 Hz, voltage between 1.2 and 3.8 V, and pulse width of 60 and 90 μs. Because they observed a trend for the benefit to wear off, cyclic stimulation with continuous stimulation during the day and off stimulation at night was preferred after the study. Adverse events included ipsilateral oscillopsia and limb myoclonus induced by low frequency-stimulation (5–35 Hz), and contralateral paresthesia induced by stimulation over 60 Hz. Three patients reported improvement in sleep with an increase in daytime vigilance.

Moro evaluated the effects of unilateral PPN DBS in six patients with Parkinson's disease with freezing of gait and postural instability. However, unlike Ferraye's study, the patients in Moro's study did not have STN DBS. The contacts used were located in the anterolateral tegmentum of the pontomesencephalic junction. PPN DBS did not provide an acute benefit, but it induced reversible and intensity- and frequency-dependent adverse effects, including contralateral paresthesia, unilateral oscillopsia, and contralateral warm sensation. Settings with frequency of 50 Hz and 70 Hz, pulse width of 60 μs, and voltage of 1.9 usually produced better motor scores. Bipolar stimulation provided better motor outcomes than monopolar stimulation. There was no significant difference in UPDRS II and III total scores and subscores for falling, freezing, or gait and balance between on and off stimulation in either on and off medication conditions during the double-blind assessment after three months and 12 months of continuous stimulation. But, during the open-label assessment, there was improvement in total UPDRS II scores (particularly subscores for freezing and fall) in the off-medication/on-stimulation state at three months and 12 months. Total motor scores and subscores for gait and postural stability (open-label assessment) also improved, but the improvement did not reach the statistical significance.

■ **COMMENTARY**

Although studies in non-human primates, previous open-label studies on PPN DBS, and the open-label part of these two most recent studies have shown that PPN DBS may improve gait and postural stability in advanced Parkinson's disease, double-blind studies did not show significant improvement in gait freezing and postural instability. Limitation of the studies include small sample size, limitation of current scoring systems for gait and postural stability, unclear onset of action when PPN DBS was turned on and wash-out period once it was turned off, and limited knowledge on the most effective anatomical location for stimulation as well as the best stimulation setting (bilateral vs unilateral stimulation, polarity, frequency, pulse width, and amplitude). ■

Camptocormia in Parkinson's Disease

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: *Camptocormia may occur in a wide variety of central and peripheral nervous system disorders, including primary muscle disease.*

Source: Margraf NG, et al. Camptocormia in idiopathic Parkinson's disease: A focal myopathy of the paravertebral muscles. *Mov Disord* (wiley.com. DOI: 10.1002/mds.22780).

CAMPTOCORMIA (CC), ABNORMAL TRUNK FLEXION APPEARing when standing or walking and disappearing when supine, has been attributed to normal aging, and a wide variety if disorders, including hysteria, spondylitis, neuromuscular disorders extending from the anterior horn cell to muscle including amyotrophic lateral sclerosis, myasthenia gravis, polymyositis, inclusion body myositis, and nemaline myopathy, to paraneoplasia, and valproate toxicity. Seen commonly in movement disorders, particularly Parkinson's disease (PD), it has been ascribed to axial dystonia.[1] Current evidence suggests that camptocormia in idiopathic PD may be myopathic in origin.

Between 2004 and 2007, 15 PD patients with CC and 15 without CC underwent comparison study encompassing detailed neurological examination including the

Unified Parkinson's Disease Rating Scale, electromyographic (EMG) study, cranial scan, serum creatine kinase measurement, magnetic resonance imaging of paravertebral muscles of the entire spinal axis with and without gadolinium, and biopsy of paravertebral muscles, the latter compared to age-matched autopsies, to explore the etiology of CC in PD. British Parkinson's Disease Society Brain Bank criteria were used to diagnose PD. Radiographic studies were evaluated by blinded neuro-radiologists. Statistical analysis included the Mann-Whitney U-test and Spearman's rank correlation coefficient.

CC occurred almost exclusively in advanced PD, occurring a median of 9.0 years after PD diagnosis, at a median of 64 years of age, with a median angle of 60° forward flexion, and equally in men and women. CC was more severe the younger the age of PD onset. Most patients (n = 13) bent forward from the onset, with 12 also reporting lateral flexion. Two began with lateral flexion, later developing anteroflexion, and no correlation was found between side of PD onset and side of CC onset. CC was also present in the seated position in 10. Back pain was reported in 13 CC patients but it predated CC in eight. No CC patient demonstrated dystonic abdominal musculature. Back pain, additional back diseases, and less dopa-sensitivity were seen significantly more in CC-PD patients compared to PD patients without CC.

Among CC patients, CK was elevated in nine, and EMG demonstrated small polyphasic myopathic motor unit potentials in eight. MRI was abnormal in all CC patients, demonstrating either bilateral asymmetrical muscle edema, which enhanced with GAD, in those with disease duration less than 12 months, or localized or asymmetrical muscle atrophy and fatty degeneration, in those with disease duration greater than 30 months. Paravertebral muscle biopsy in 12 CC patients, obtained from the most affected muscles based on MRI scan, was myopathic in all, with increased connective tissue, internal nuclei, variability of fiber size, variable expression of atrophic and hypertrophic fibers, and fiber splitting. Myopathic EMG, MRI, or biopsy abnormalities were not seen in the non-CC-PD group. Corsets, increased carbidopa/levodopa dosage, and oral corticosteroid medication were of no benefit. CC in PD appears to be a focal progressive myopathy of the paravertebral muscles.

■ **COMMENTARY**

Protirelin tartrate (PT, thyrotropin-releasing hormone tartrate), believed to act by regulating excitatory amino acids or glucose metabolism, has been used, primarily in Japan, for the treatment of a variety of ataxic disorders including hereditary spinocerebellar degeneration and multiple system atrophy (MSA). Administered to a 68-year-old woman with camptocormia associated with MSA, camptocormia was significantly improved by the second day of treatment.[2] At Weill Cornell Medical Center, an 80-year-old man with camptocormia and found to have 3.9 × 3.8 × 3.9 cm dural-based extra-axial meningioma within the right frontal region with extensive surrounding vasogenic edema, resulting in approximately 6 mm of right-to-left subfalcine herniation. Surgical resection of the tumor resolved the camptocormia. Camptocormia has a broad differential and both supratentorial and infratentorial causes must be pursued. ■

References

1. Bloch F, et al. Parkinson's disease with camptocormia. *J Neurol Neurosurg Psychiatry* 2006;77:1223–1228.
2. Takei A, et al. Amelioration of subacute camptocormia in multiple system atrophy by protirelin tartrate. *Movement Dis* 2009:24;2022-2023

CME Questions

41. All of the following are common features of CSS except:

a. Asthma

b. Peripheral eosinophilia

c. CNS vasculitis

d. Peripheral neuropathy

e. Mononeuritis multiplex

CME Objectives

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

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

CME Instructions

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

42. Which of the following genetic factors may reduce the risk of developing Alzheimer's disease?

a. Apolipoprotein E2 allele

b. V405 allele of the cholesterol ester transfer protein gene

c. Apolipoprotein E4 allele

d. a, b, and c

e. a and b only

43. Familial hemiplegic migraine:

a. Is manifested solely by headache and hemiparesis.

b. Can be associated with cerebral edema after mild head trauma.

c. Has been studied in a knock-out mouse model.

d. Has an autosomal recessive inheritance pattern.

e. Is a monogenetic syndrome that is diagnosed most commonly in perimenopausal women.

44. Which statement is correct?

a. PPN is located in basal ganglia.

b. PPN belongs to mesencephalic reticular formation

c. Double-blind studies showed that PPN DBS improved motor function, gait and postural stability.

d. Open-label studies showed that PPN DBS did not improve gait and postural stability.

e. PPN DBS is a widely accepted treatment for advanced Parkinson's disease with freezing of gait.

45. Camptocormia may be due to:

a. Primary myopathy

b. Frontal meningioma

c. Hysteria

d. Myasthenia

e. All of the above

46. Intermittent fasting increases risk and severity of ischemic stroke.

a. True

b. False

Answers: 41. c, 42. e, 43. b, 44. b, 45. e, 46. b

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.*

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

Intermittent fasting may reduce the risk and consequences of stroke in younger, rather than older animals

Arumugam TV, et al. Age and energy intake interact to modify cell stress pathways and stroke outcome. *Ann Neurol* 2010;67:41–52.

Age and obesity are known to be risk factors for the development of ischemic stroke, but it is unknown how these factors may influence the degree of brain injury or recovery. Epidemiological studies suggest that calorie-restricted diets that result in very low body-mass index may extend life. In a study using a mouse model of stroke, using middle cerebral artery occlusion, these investigators studied the effects of age, by looking at young, middle-aged, and old animals, and the impact of intermitted fasting on the degree of brain injury from stroke. In addition to severity of stroke and outcome, the investigators also measured a variety of inflammatory and pro-aptotic mediators in the fasting and control groups, to determine if fasting influenced the production of mediators that increased cell death.

Mortality from focal ischemic stroke was increased by advancing age, but decreased by fasting. Intermittent fasting reduced brain injury and functional impairment in the younger animals but not in the older ones. The basal and poststroke levels of neurotrophic factors, protein chaperones (heat shock protein 70 and glucose regulated protein 78), and the antioxidant enzyme heme oxygenase-1 were decreased, whereas levels of inflammatory cytokines were increased in the cerebral cortex and striatum of old mice compared with younger mice. Intermittent fasting increased levels of protective proteins and decreased levels of inflammatory cytokines in the younger animals, but not in the older ones.

Modern medical therapy, especially the use of statins, can slow carotid artery atherosclerosis progression and subsequent stroke risk.

Spence JD, et al. Effects of intensive medical therapy on microemboli

and cardiovascular risk in asymptomatic carotid stenosis. *Arch Neurol* 2010;67:180-186.

ASYMPTOMATIC CAROTID ARTERY STENOSIS (ACS) >60% may be treated with endarterectomy or stenting, but the real benefit of these interventions over modern medical therapy is unknown. When the ACS Trial was performed, there were few medical therapies available, and the potent statins were not used in the medical arm. Therefore, there is great interest in determining if modern medical therapy would now compare favorably to surgical intervention, but a new randomized trial is not likely to be initiated.

With this in mind, the investigators studied a cohort of 468 ACS patients, looking at microemboli by TCD, cardiovascular events, rate of carotid atherosclerosis progression, and medical therapies before and after 2003. Microemboli were present in 12.6% before 2003 and 3.7% since 2003. Since 2003, there have been significantly fewer cardiovascular events among patients with ACS: 17.6% had stroke, death, myocardial infarction, or carotid endarterectomy for symptoms before 2003, vs 5.6% since 2003. The rate of carotid plaque progression in the first year of follow-up has declined from 69 mm2 (SD, 96 mm2) to 23 mm2 (SD, 86 mm2). The changes in outcomes coincided with improved control of plasma lipids, and more aggressive management of hypertension. Modern medical management will continue to reduce the risk of stroke in patients with ACS and very few will require a surgical intervention.

Carotid endarterectomy remains the gold-standard in the treatment of symptomatic carotid artery stenosis

International Carotid Stenting Study Investigators. Carotid artery stenting compared with endarterectomy in patients with symptomatic carotid stenosis (International Carotid Stenting Study): An interim analysis of a randomised controlled trial. *Lancet* (early online publication) 26 February 2010 doi:10.1016/S0140-6736(10)60239-5.

THE ICSS WAS A MULTICENTER, RANDOMIZED TRIAL DESIGNED to directly compare the short-term safety and long-term efficacy of carotid artery stenting (CAS) compared to carotid artery endarterectomy (CEA) in patients with symptomatic carotid artery stenosis. The three-year outcome data is still being analyzed; this report gives 120 day safety data for the two groups.

The trial enrolled 1,713 patients (stenting group, n = 855; endarterectomy group, n = 858). Between randomisation and 120 days, there were 34 (4•0%) events of disabling stroke or death in the stenting group compared with 27 (3•2%) events in the endarterectomy group (hazard ratio [HR] 1•28, 95% CI 0•77–2•11). The incidence of stroke, death, or procedural myocardial infarction was 8•5% in the stenting group compared with 5•2% in the endarterectomy group (72 vs 44 events; HR 1•69, 1•16–2•45, p = 0•006). Risks of any stroke (65 vs 35 events; HR 1•92, 1•27–2•89) and all-cause death (19 vs 7 events; HR 2•76, 1•16–6•56) were higher in the stenting group than in the endarterectomy group. Three procedural myocardial infarctions were recorded in the stenting group, all of which were fatal, compared with four, all non-fatal, in the endarterectomy group. The initial safety data from this trial shows CEA to be favorable compared to CAS. However, the primary efficacy measure, outcome at three years, has yet to be analyzed and reported.

One day after the ICSS data was reported, the Carotid Revascularization Endarterectomy vs Stenting Trial (CREST) primary results were presented at the International Stroke Meeting in Texas (abstract # 197). The overall conclusion of the CREST trial was that CEA and CAS were comparable in terms of safety and efficacy. However, we will await publication of the results before making any further comments.

Obstructive sleep apnea after stroke may be missed

Arzt M, et al. Dissociation of obstructive sleep apnea from hypersomnolence and obesity in patients with stroke. *Stroke* 2010;DOI: 10.1161/STROKEAHA.109.566463.

SLEEP-DISORDERED BREATHING IS A RISK FACTOR FOR STROKE and other cardiovascular diseases, and the development of obstructive sleep apnea (OSA) after stroke is a significant risk factor for recurrent stroke and death. However, many stroke patients with this disorder are not recognized, and this study attempted to determine the clinical characteristics that would lead to a correct diagnosis of OSA.

Polysomnography was performed on 96 consecutive stroke patients admitted to a rehabilitation unit, and compared with a large community control group for severity of daytime sleepiness (Epworth Scale), body mass index, and severity of OSA. Compared with the community sample, patients with stroke with OSA had significantly lower Epworth Sleepiness Scale scores and body mass index for mild, moderate, and severe degrees of OSA. Therefore, many stroke patients who have OSA will be missed if they are screened with the usual tools to identify high risk groups. A high index of suspicion should be used when evaluating a stroke patient for sleep-disordered breathing.

In Future Issues: **Concussion and Traumatic Brain Injury**

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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BP response of atenolol vs HCTZ

Source: Beitelshees AL, et al. Comparison of office, ambulatory, and home blood pressure antihypertensive response to atenolol and hydrochlorthiazide. *J Clin Hypertens* 2010;12:14-21.

In untreated subjects with hypertension (HTN), findings on 24-hour ambulatory blood pressure monitoring (ABPM) or home blood pressure monitoring (HBP) have been found to provide better indication of risk than office blood pressure (OBP). On-treatment BP measurement using the same techniques shows similar associations: ABPM is better than HBP, which is better than OBP for risk prediction. Since not all patients can be availed of ABPM, HBP monitoring has received increased advocacy.

HCTZ and atenolol (ATN) are two of the most commonly prescribed antihypertensive agents in the United States. Beitelshees et al performed a randomized controlled trial to assess the relative accuracy of OBP and HBP compared to the gold standard ABPM in subjects (n = 418) treated with HCTZ, atenolol, or the combination.

For both systolic and diastolic BP, correlation with ABPM was significantly better for HBP than OBP. For example, OBP overestimated treatment effects on SBP by 4.6 mm Hg compared with HBP. Recent HTN consensus groups have endorsed routine HBP monitoring; these data support the role of HBP monitoring as a better risk predictor than OBP. ■

Ipratropium and CV events in COPD

Source: Ogale SS, et al. Cardiovascular events associated with ipratropium bromide in COPD. *Chest* 2010;137:13-19.

Bronchodilators (i.e., inhaled beta agonists and anticholinergics) are the foundation of symptomatic care for COPD. Metered-dose inhaler administration of ipratropium (IPR) is generally very well tolerated, and associated with few, if any, adverse symptoms. Nonetheless, there remains some conflict about the cardiovascular safety of anticholinergic bronchodilators in COPD. One meta-analysis suggested as much as a 53% increased relative risk for MI in COPD patients treated with IPR; in contrast, a large randomized prospective trial with tiotropium (n = 6000, approximately) did not find any signal for increased cardiovascular events.

Ogale et al performed a cohort study comprised of newly diagnosed COPD patients (n = 82,717) attending an Illinois VA hospital.

Risk for a cardiovascular event was 29% higher in COPD patients treated with IPR than comparators. Risk was time-related: Those with at least a 6-month interval since last exposure to an anticholinergic were not at greater risk. The mechanism by which anticholinergics might increase cardiovascular risk is not clear, although a dose-response relationship between IPR and supraventricular tachyarrhythmia incidence noted in the Lung Health Study intimates a possible connection. ■

Kidney function, proteinuria, and adverse outcomes

Source: Hemmelgarn BR, et al. Relations between kidney function, proteinuria, and adverse outcomes. *JAMA* 2010;303:423-429.

Staging of chronic kidney disease (CKD) is based primarily upon estimated GFR. Proteinuria (PRO) is a strong marker for kidney disease, yet its severity is not included in current risk stratification schemes, which are instead driven by GFR. Indeed, the majority (75%) of proteinuric patients do not have a GFR < 60 mg/min. Intuitively, since either PRO or stage of CKD predicts risk, the combination of the two might be an even better risk predictor.

To study the relationship of CKD, PRO, or the combination with outcomes, data from 920,985 Canadian adults was analyzed. Persons with end-stage renal disease at study inception were excluded.

Over 35 months of follow-up, for each decrement in GFR, all-cause mortality, MI, and end-stage renal disease increased. Within each quartile of GFR, progressively increasing levels of proteinuria (normal, mild, heavy) were associated with increased risk. Persons with the very lowest GFR (i.e., most advanced kidney disease), however, experienced less relative impact per degree of proteinuria; in other words, adverse outcomes are more compounded by proteinuria in CKD 2-4 than CKD 5.

The recent adoption of a standardized staging system for CKD is a major step forward. These data suggest that future stratification methods would benefit from inclusion of proteinuria as well as GFR. ■

Remission of diabetes with bariatric surgery

Source: Wilson JB, Pories WJ. Durable remission of diabetes after bariatric surgery: What is the underlying pathway? *Insulin* 2010;5:46-55.

THE BURGEONING POPULATION OF individuals with type 2 diabetes (DM2) corresponds to a parallel increase in obesity. Although bariatric surgery produces prompt and sustainable weight loss, the post-surgical rapidity with which derangements of diabetes resolve defies explanation by weight loss alone.

Bariatric surgical procedures that eliminate food contact with the duodenum and jejunum — as opposed to gastric banding type procedures — produce not only substantial weight loss, but also provide remission of DM2 within days. Indeed, as many as 80% of DM2 patients leave the hospital with no diabetes medications, and more than 75% remain DM2-free 5 years later. Similar reversion to normal glucose handling has also been seen in IGT patients who have bypass surgery.

Post-surgical benefits of bariatric surgery include resumption of normal menstrual function, BP and lipid improvements, and reductions in diabetes-related mortality. Studies of gastric banding conclude that weight loss is responsible for these favorable outcomes; in contrast, bariatric bypass surgery, although enjoying benefits attributable to weight loss, has other operant mechanisms: One report of intestinal bypass in lean DM2 individuals found resolution of diabetes without weight loss.

The GI tract has been increasingly recognized as a critical player in glucose dysregulation, as evidenced by evolution of the incretin mimetics and DPP-4 inhibitors. Resolution of dysglycemia within a few days — prior to meaningful weight loss — is characteristic of bariatric bypass surgery. ■

Inhaled corticosteroids and COPD exacerbations

Source: Agarwal R, et al. Inhaled corticosteroids vs placebo for preventing COPD exacerbations: A systematic review and metaregression of randomized controlled trials. *Chest* 2010; 137:318-325.

ACUTE EXACERBATIONS OF COPD (AECOPD) are costly to patients. Not only is the symptomatic deterioration and commonplace requirement for hospitalization burdensome, but an AECOPD is typically followed by loss of pulmonary function that does not return. Additionally, mortality from hospitalized AE-COPD has been reported to be as high as 10%.

We have no known disease-modifying pharmacotherapy for COPD. Although symptom improvement is considerable from bronchodilators and inhaled corticosteroids (ICS), they do not change disease progression. Short of that outcome, reduction in AE-COPD is a worthy goal to seek.

Agarwal et al reviewed data from 11 placebo-controlled COPD trials (n = 8164) employing ICS to examine the impact upon AE-COPD. Overall, ICS use was associated with an 18% relative risk reduction in AE-COPD; this beneficial effect was driven primarily by persons with an FEV1 < 50%.

Recent meta-analyses have shown an increased risk of pneumonia in COPD patients receiving ICS. Because the risk reduction for AE-COPD is modest, careful consideration to the risk-benefit balance of ICS use is appropriate. ■

Non-alcoholic fatty liver disease in Japanese patients

Source: Hamaguchi E, et al. Histological course of nonalcoholic fatty liver disease in Japanese patients. Tight glycemic control, rather than weight reduction, ameliorates liver fibrosis. *Diabetes Care* 2010;33:284-286.

IN THE UNITED STATES, DIABETES AND metabolic syndrome are the disorders most commonly associated with nonalcoholic fatty liver diseases (NAFLD). Because obesity, dyslipidemia, hypertension, and insulin resistance are typical operative components of these disorders, it is difficult to make a clear attribution about which is the primary culprit leading to NAFLD.

Japanese subjects do not demonstrate the same degree of obesity as Americans. Study of NAFLD in this population might provide insight about the primary drivers of pathology.

Serial liver biopsies on two occasions were obtained from 39 Japanese NAFLD patients over a mean follow-up of 2.4 years. During this interval, NAFLD improved in 30.7%, worsened in 28.2%, and was unchanged in 41%.

Improvement in glycemic control, as measured by A1C, was the best predictor of NAFLD improvement. Transforming growth factor-beta and plasminogen activator inhibitor type 1 are known regulators of hepatic fibrosis, both of which are stimulated by high glucose levels. ■

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Thiazolidinediones and Risk of Heart Failure

In this issue: FDA is reviewing safety of TZDs; SSRI use with tamoxifen; Metformin smells like fish; FDA Actions.

FDA reviews TZD safety

Thiazolidinediones (TZDs) have been under intense scrutiny in recent years after rosiglitazone (Avandia®) was linked to increased cardiovascular morbidity and mortality in several studies. In recent weeks, *The New York Times* has reported that some FDA staffers are recommending that rosiglitazone be removed from the market. According to the story in the *Times*, a "confidential government report" states that about 500 heart attacks and 300 cases of heart failure per month could be averted if patients were switched from rosiglitazone to pioglitazone (Actos®). Congress has even gotten involved, specifically the Senate's Committee on Finance, which in January issued a 350-page report on rosiglitazone, focusing on GlaxoSmithKline's handling of evidence of possible cardiac risks associated with use of the drug. Now the American Heart Association and the American College of Cardiology have weighed in on the issue suggesting there is insufficient evidence to support the use of pioglitazone over rosiglitazone and that both drugs increase the risk for heart failure and should not be initiated in patients with class III/IV heart failure. They further state that the drugs should not be used with an expectation of benefit with respect to ischemic heart disease events (*Circulation*, published on-line Feb. 23, 2010). Meanwhile, the FDA web site reports that the Agency is reviewing data on rosiglitazone and is planning a public meeting in July 2010 to present all known heart-related safety data on the drug and provide an updated assessment of the risks and benefits of rosiglitazone and the treatment of type 2 diabetes. ■

SSRI use with tamoxifen

The SSRI paroxetine (Paxil®) reduces the effect of tamoxifen in women with breast cancer leading to higher breast cancer mortality according to a new study in the *British Medical Journal*. Concern about SSRIs interfering with the metabolism of tamoxifen was raised last June at the American Society of Clinical Oncology meeting. Tamoxifen is converted from its prodrug to the active metabolite via the cytochrome P450 pathway, specifically CYP2D6. Paroxetine is an exceptionally strong inhibitor of CYP2D6, the strongest inhibitor of all the SSRIs. In the study, Canadian researchers looked at more than 2400 women from Ontario treated with tamoxifen for breast cancer along with a single SSRI. After adjustment for confounders, absolute increases of 25%, 50%, and 75% in the proportion of time on tamoxifen with overlapping use of paroxetine were associated with 24%, 54%, and 91% increases in the risk

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of death from breast cancer, respectively ($P < 0.05$, for each comparison). No such risk was seen with any other antidepressant. The authors conclude that paroxetine use during tamoxifen treatments is associated with an increased risk of death from breast cancer, supporting the hypothesis that paroxetine can reduce or abolish the benefit of tamoxifen in women with breast cancer (*BMJ* 2010;340:c693). The study is important because up to one-quarter of women diagnosed with breast cancer experience a depressive disorder, and antidepressants are commonly used during tamoxifen treatment for not only depression, but also for treatment of hot flashes and other symptoms. It is evident that paroxetine should never be prescribed to women taking tamoxifen for treatment of breast cancer and that preference should be given to antidepressants that show little or no inhibition of CYP2D6. Among the SSRIs, the strongest inhibitors of CYP2D6 besides paroxetine are fluoxetine (Prozac®), duloxetine (Cymbalta®), and to a lesser extent sertraline (Zoloft®). Among non-SSRI antidepressants, bupropion (Wellbutrin®) also is a strong CYP2D6 inhibitor. Drugs that are not inhibitors of the enzyme include citalopram (Celexa®) and venlafaxine (Effexor®). ■

Generic metformin smells fishy?

If your patients tell you their pills smell like fish, they may be taking generic metformin. A letter to the *Annals of Internal Medicine* describes two patients who stopped taking generic metformin because of a fishy taste that caused nausea. The fishy smell is a property of metformin and is well known to pharmacists. Apparently the film-coated extended-release formulations have less smell and may be better tolerated (*Ann Intern Med* 2010;152:267-268). ■

FDA actions

A new FDA warning states that **long-acting beta agonists** (LABAs) should never be used alone in the treatment of asthma in children or adults. The LABAs salmeterol (Serevent®) and formoterol (Foradil®) have been associated with severe worsening of symptoms when used without a controller medication such as an inhaled corticosteroid. Both products will be required to include warnings on the product label that states:

- Use of LABAs is contraindicated without the use of an asthma controller medication;
- LABAs should only be used long term in patients whose asthma cannot be adequately controlled on asthma controller medications;
- LABAs should be used for the shortest duration of time required to achieve control, and should be discontinued once asthma control is achieved;
- Pediatric and adolescent patients who require an LABA in addition to an inhaled corticosteroid should use a combination product containing both an inhaled steroid and a LABA to ensure compliance with both medications.

The FDA has approved **rosuvastatin (Crestor®)** for primary prevention in patients without elevated LDL-cholesterol but who have an elevated C-reactive protein (2 mg/L or higher) and at least one additional cardiovascular risk factors such as low HDL, hypertension, or family history of premature heart disease. The approval was based on the JUPITER trial, which showed a 44% reduced relative risk of cardiovascular events in patients with normal LDL cholesterol but elevated CRP.

The FDA has approved a new **pneumococcal vaccine** for infants and children. Wyeth Pharmaceuticals' **Prevnar 13™** is a 13-valent conjugate vaccine that will replace the currently available 7-valent Prevnar®. It is approved for the prevention of invasive disease caused by 13 different serotypes of *S. pneumoniae*.

The FDA has approved the **monoclonal antibody rituximab (Rituxan®)** to treat certain patients with chronic lymphocytic leukemia (CLL). Rituximab is approved for CLL patients who are starting chemotherapy for the first time and also for those who have not responded to other CLL therapies. It is administered with fludarabine and cyclophosphamide for the treatment of CLL. Rituximab is manufactured by Genentech.

The FDA is initiating a risk-management program for **erythropoiesis-stimulating agents** (ESAs) for the treatment of chemotherapy-related anemia. The drugs, which include epoetin alfa (Procrit®, Epogen®) and darbepoetin alfa (Aranesp®), have been associated with accelerated tumor growth and higher mortality rates in some cancer patients. The Risk Evaluation and Medication Strategy (REMS) requires that patients receive a medication guide on safety issues associated with the drugs and requires training and certification of health care professionals who administer chemotherapy to patients with cancer and counseling of patient regarding the risks of the drugs. The REMS does not currently apply to patients being treated with an ESA for anemia due to other conditions, specifically renal failure. ■