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INSIDE

Financial Disclosure:
Neurology Alert's editor in chief, Matthew Fink, MD, reports no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.
Peer reviewer M. Flint Beal, MD, reports no consultant, stockholder, speaker's bureau, research, or other financial relationship with any company having ties to this field of study.

Can We Identify Pre-Motor Parkinson's Disease in LRRK2 Carriers?

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Associate Professor of Neurology and Neuroscience, Weill Cornell Medical Center

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

Synopsis: *Evaluation of non-parkinsonian carriers of the LRRK2 mutation associated with Parkinson's disease supports a model of pre-motor symptomatology, including impaired color discrimination and constipation, that could be related to pathology developing prior to that in the substantia nigra.*

Source: Marras C, et al. Phenotype in Parkinsonian and nonparkinsonian LRRK2 G2019S mutation carriers. *Neurology* 2011;77:325-333.

This international study focuses on individuals with Parkinson's disease (PD) due to the G2019S LRRK2 mutation, a cause of both familial and sporadic PD, and provides the most detailed description to date of their motor and non-motor phenotypes. Fifteen unrelated probands (from sites in Canada, the United States, Brazil, and Germany) were compared with 54 first-degree relatives with identical LRRK2 mutations (25 of whom had PD), 53 relatives without the mutation and without PD, 84 individuals with idiopathic PD (iPD), and 112 unrelated controls (the iPD and control groups were recruited at German sites only). Enrolled subjects underwent neurologic exam, but also a careful assessment of features believed to constitute a premotor constellation of symptoms related to possible early PD pathology outside of the substantia nigra. Premotor symptoms include impaired olfaction and color vision, anxiety, and depression. In terms of motor features, those with LRRK2-PD had a tremor presentation more often than iPD. They also had better olfactory identification, worse color discrimination as judged by the Farnsworth-Munsell 100-Hue test, and higher depression scores on the Beck Depression Inventory scale. The most fascinating finding, however, is that LRRK2 G2019S non-manifesting carri-

VOLUME 30 • NUMBER 1 • SEPTEMBER 2011 • PAGES 1-8

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ers also were found to have significant differences in non-motor features compared with control subjects, including worse constipation and visual color discrimination, as well as mildly higher scores on the Unified Parkinson's Disease Rating Scale that objectively evaluates PD signs and symptoms (UPDRS). This was also true of family members who did not carry the LRRK2 gene mutation, raising the question of other as yet unknown factors contributing to PD risk in these families.

■ COMMENTARY

LRRK2 mutations account for approximately 4% of familial and 1% of sporadic cases of PD, although in certain populations they may be more important: For example, in North African Arabs, LRRK2 mutations have been detected in approximately 40% of individuals with sporadic PD. Penetrance is incomplete, and age-dependent. Both phenotypic and pathologic heterogeneity due to this mutation remain a field of intense interest, and Marras and colleagues therefore provide a significant contribution in their detailed phenotypic descriptions. Importantly, the authors demonstrate that despite minor phenotypic differences, the LRRK2 G2019S mutation (which is the most common pathogenic LRRK2 mutation) leads to a phenotype largely indistinguishable on a clinical basis from idiopathic PD. It is therefore hoped that this population will provide information that may be extended to the larger population with "idiopathic" PD, and in particular that studying non-parkinsonian LRRK2 G2019S carriers will shed light upon development of clinical PD. Therefore, the most intriguing finding is that non-manifesting LRRK2 G2019S carriers have subtle but measurable differences from controls in color discrimination, constipation, and in UPDRS scores. These could potentially represent a "pre-motor" or "pre-diagnostic" phenotype, of use for risk stratification in the future. Unfortunately, differences in recruitment sites between subject groups (and therefore potential differences in examiners and assessments) limits interpretation of findings. In addition, the authors had to make statistical adjustments for age and disease duration, since those with LRRK2-associated PD were younger and had a shorter disease duration than enrollees with iPD. However, a companion article by Saunders-Pullman and colleagues examining 31 individuals with LRRK2 G2019S-related PD recruited within New York City provides data supporting the possibility of a "pre-motor" phenotype detectable in a subset of mutation carriers, in this case olfactory dysfunction.[1] Longitudinal data will be important to see which of these carriers goes on to develop PD (or another) phenotype, but the present data support the notion that assessment of non-motor features may eventually provide a logical data-driven screening strategy for individuals at risk for PD. Identification of such a group is imperative if we are to test preventive interventions (for example, exercise, diet, and pharmacologic neuroprotectants). Finally, with efforts to provide broad public access to genetic testing, including the LRRK2 gene, the clinician will be increasingly faced with worried individuals seeking guidance on their neurologic risk. It is therefore important that expanded and longitudinal studies be pursued, in order to provide meaningful information on risk to our patients. ■

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1. Saunders-Pullman R, et al. Olfactory dysfunction in LRRK2 G2019S mutation carriers. *Neurology* 2011;77:319-324.

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media, a division of Thompson Media Group, LLC, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

EXECUTIVE EDITOR: Leslie G. Coplin
MANAGING EDITOR: Neill L. Kimball

GST Registration Number: R128870672.

Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 105109, Atlanta, GA 30348.

Subscriber Information

Customer Service: 1-800-688-2421.
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World-Wide Web: www.ahcmedia.com

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1 year with free AMA Category 1 credits: $319
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Myopathic Side Effects from Statin Use

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: *Symptoms of muscle pain and discomfort are common with statin use, but weakness and creatine kinase elevation are unusual.*

Source: El-Salem K, et al. Prevalence and risk factors of muscle complications secondary to statins. *Muscle Nerve* 2011;onlinelibrary.wiley.com/doi/10.1002/mus.22205/pdf.

How frequent are statin-induced adverse side effects and which factors may predispose to their development? At King Abdullah University Hospital, Irbid, Jordan, a prospective comparative study was undertaken to answer these questions, and, over a 12-month period, all patients who received statin therapy were invited to participate. Information was gathered regarding the dose, form, and duration of statin administration; other concomitant medications; as well as symptoms of muscle pain, cramps, stiffness, fatigue, and weakness during or before statin initiation. Creatine kinase levels were measured and all patients underwent neurological examination. Patients were matched with a control group of 85 persons recruited from the General Neurology and Medicine clinics who were not on statins and who presented with minor problems, usually headaches. Statistical analysis was provided using the Statistical Package for Social Sciences software (SPSS, version 11.5, Chicago. Inc), with Chi-square and independent sample t test applied as indicated. Calculation of crude odds ratios and their 95% confidence intervals, logistic regression, and adjusted odds ratios completed the analysis, and P values < 0.05 were considered statistically significant.

Among 345 patients on statins, including pravastatin (Pravachol), fluvastatin (Lescol) and rosuvastatin (Crestor), but most frequently atorvastatin (Lipitor) and simvastatin (Zocor), mean age was 59 years, and 60% were male. Compared to controls, statin patients were more likely to have higher body mass index (BMI), diabetes, and a history of stroke. Muscle symptoms (pain, tenderness, fatigue, stiffness, cramps, and weakness) were reported in 21% vs 5.9% of controls, whereas on examination, weakness, always mild, bilateral, proximal more than distal, and affecting arms and legs, was found in 15% of those who reported muscle symptoms. Creatine kinase levels were elevated in only two patients, both with weakness on examination and only three- to four-fold above normal. Symptoms were statistically more likely to occur in patients who were on statins for > 10 months, had diabetes, a history of stroke, lower BMI, and were age 60 years or older. No correlation with adverse symptomatology was found with respect to gender, statin dose, kidney, liver, cardiovascular, or thyroid disease. Muscle symptoms are more common than usually appreciated following statin administration and certain patient subpopulations appear to be particularly susceptible.

■ COMMENTARY

Statin-induced myopathy is thought to result from inhibition of mevalonate synthesis, with consequent depletion of mevalonate metabolites including cholesterol, isoprenoids, and ubiquinone (coenzyme Q10). Cholesterol depletion adversely affects cell membranes, isoprenoid depletion adversely affects intracellular signaling, and ubiquinone deficiency impairs mitochondrial respiratory chain function.[1] Genetic factors also play a role, as demonstrated by the PRIMO study where family history was one of the strongest predictors for statin-induced muscle pain.[2]

What should be done for patients who develop muscle symptoms while on statins? If complaints are tolerable and creatine kinase levels are normal or only mildly elevated (< 5-fold upper limit of normal), statins may be continued at the same or a reduced dose, using the patients' symptoms as the guide to continue or halt therapy. If muscle complaints are tolerable but creatine kinase levels are more than five-fold above the upper limit of normal, or if symptoms are intolerable regardless of creatine kinase levels, it is recommended that statins be discontinued and, following recovery, their use may be carefully reconsidered. Either the same statin at a lower dose or a different statin may be offered. If symptoms recur with multiple statins, alternative-lipid lowering therapy should be initiated.[3] ■

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3. Harper CR, Jacobson TA. Evidence-based management of statin myopathy. *Curr Atheroscler Rep* 2010;12:322–330.

Does Higher Vitamin D Intake During Pregnancy Reduce the Risk of Multiple Sclerosis in Offspring?

ABSTRACT & COMMENTARY

By Jai S. Perumal, MD

Assistant Professor of Neurology, Weill Cornell Medical College

Dr Perumal is a consultant for Biogen Idec, and is on the speakers bureau for Teva and Biogen Idec.

Synopsis: *Based on data from the Nurses' Health Study II, the authors report that higher maternal intake of vitamin D during pregnancy may be associated with a lower risk of multiple sclerosis in their children.*

Source: Mirzaei F, et al. Gestational vitamin D and the risk of multiple sclerosis in offspring. *Ann Neurol* 2011;70:30-40.

Stroke Alert: A Review of Current Clinical Stroke Literature

By Dara Jamieson, *MD, Associate Professor of Clinical Neurology, Weill Cornell Medical College*

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

Hypertension and the Pregnant Woman: An Increasing Risk for Stroke Now and in the Future

Synopsis: *The incidence of stroke associated with pregnancy, especially cerebral venous sinus thrombosis, is increasing, with hypertension as a major culprit. Hypertension as a complication of pregnancy increases a woman's risk of stroke in the future.*

Sources: Kuklina EV, et al. Trends in pregnancy hospitalizations that included a stroke in the United States from 1994 to 2007: Reasons for concern? *Stroke* 2011; Jul 28. [Epub ahead of print]
Wasay M, et al. Predictors of cerebral venous thrombosis and arterial ischemic stroke in young Asian Women. *J Stroke Cerebrovasc Dis* 2011; Apr 19. [Epub ahead of print]
Wang I-K, et al. Hypertensive disorders in pregnancy and preterm delivery and subsequent stroke in Asian women: A retrospective cohort study. *Stroke* 2011;42:716-721.

THE REPORT OF KUKLINA ET AL ANALYZED STROKE HOSPITALIZATIONS for women in the antenatal, delivery, and postpartum periods from 1994-1995 and from 2006-2007. Hospital discharge data were obtained from the Nationwide Inpatient Sample, developed as part of the Healthcare Cost and Utilization Project sponsored by the Agency for Healthcare Research and Quality. The number of pregnancy-related stroke hospitalizations grew during that period by 54%, increasing from ~4000 in 1994-1995, to ~6000 hospitalizations in 2006-2007. Between the periods of 1994-1995 and 2006-2007, the rate of any stroke — subarachnoid hemorrhage, intracerebral hemorrhage, acute ischemic stroke (AIS), transient ischemic attack, cerebral venous thrombosis (CVT), or unspecified — among antenatal hospitalizations increased by 47% (from 0.15 to 0.22 per 1000 deliveries) and among postpartum hospitalizations by 83% (from 0.12 to 0.22 per 1000 deliveries). At the end of the study period (2006-2007), the overall prevalence of pregnancy-related stroke hospitalizations was 0.71 per 1000 delivery hospitalizations. Hypertensive disorders were common in up to 28% of pregnancy-related stroke hospitalizations in 1994-1995. This increased to up to 41% in 2006-2007. In 1994-1995, up to 16% of pregnancy-related stroke hospitalizations were complicated by heart disease, not different from the up to 15% of hospitalizations in the 2006-2007 period. In 2006-2007, 32% and 53% of antenatal and postpartum hospitalizations with stroke, respectively, had concurrent hypertensive disorders or heart disease. Changes in the prevalence of these two conditions, especially hypertension, from 1994-1995 to 2006-2007, explained almost all of the increase in postpartum hospitalizations with stroke during the period between the years studied. Specific stroke subtypes were analyzed over the time period. In the an-

THERE IS GROWING EVIDENCE THAT VITAMIN D EXPOSURE IS inversely associated with the risk of developing multiple sclerosis (MS) and the risk of relapses in patients with established disease. Both epidemiological studies and experimental data from animal models of MS support a protective role of vitamin D. Putative immune modulatory mechanisms for these effects have been proposed as well. The present study by Mirzaei et al takes this concept of "protection" further and examines the influence of gestational vitamin D on the subsequent risk of MS in the offspring.

The Nurses' Health Study II was a cohort of 116,430 female, registered nurses between the ages of 25-42 years, which began in 1989. At baseline and at subsequent biennial follow-up, the nurses provided information on demographics, lifestyle, health-related factors, and any newly diagnosed diseases including MS. The Nurses' Mothers Study began in 2001 when the Nurses' Health Study II participants free of cancer were requested for permission to send out questionnaires to their mothers. This was restricted to nurses with living biological mothers free of debilitating disease. The information collected from the mothers included diet during pregnancy, demographics, and lifestyle experiences; 35,794 nurses' mothers completed the questionnaire. The authors of this study assessed maternal exposure to different sources of vitamin D, including fortified milk intake and dietary vitamin D and predicted serum 25(OH)D. The mothers reported their milk intake by choosing one of seven categories ranging from never to four or more glasses/day. The total dietary vitamin D intake from food was calculated by summing up the vitamin D from each of the vitamin D containing food the mothers had reported to have taken. Direct serum 25(OH) measurements were not available. Predicted serum 25(OH)D was calculated using a prediction model factoring in several variables that influence vitamin D lev-

Stroke Alert (continued)

tenatal group, the rate of CVT almost doubled between 1994-1995 and 2006-2007, and in the postpartum group, the rate of hemorrhagic stroke quadrupled.

A cohort study by Wasay et al studied Asian women, aged 15-45 years, with a diagnosis of first-ever symptomatic AIS (754 women) or CVT (204 women) confirmed by brain imaging. The patients with CVT had a mean age of 29 years. Pregnancy or postpartum state (49 patients; 24%) was the most common predisposing factor for CVT. On multivariate analysis, postpartum state and hemorrhagic infarct were the strongest predictors of CVT ($P < 0.001$). Strong predictors of AIS in young women included more traditional vascular risk factors of age over 36 years, diabetes, hypertension, dyslipidemia, recent myocardial infarction, electrocardiogram abnormalities, and blood glucose level > 150 mg/dL. While mortality was similar with CVT and AIS, neurological recovery was significantly better for patients with CVT than for those with AIS.

In a cohort study, Wang I-K et al investigated the risk of future stroke associated with hypertensive disorders in pregnancy (HDP) in 1092 pregnant Asian women (age 15-40 years) with newly diagnosed HDP from 2000-2004, as compared to 4715 randomly selected women without HDP. Both cohorts were followed until the end of 2008 to measure the incidence of future stroke of unspecified type. The HDP cohort had a higher incidence of stroke than the non-HDP cohort (30.1 vs 12.8 per 10,000 person-years), with an overall adjusted hazard ratio of 2.04 (95% confidence interval, 1.18-3.51) for stroke. Pregnant adolescents and older women with HDP had a higher risk of future stroke than did pregnant women aged 25 to 29 years. Preterm delivery, in combination with HDP, increased the risk of future stroke by 3.22-fold.

■ COMMENTARY

Women of reproductive age have an increased risk of stroke as compared to men of the same age. Oral contraceptives have been cited as contributing to this risk; however, pregnancy is an increasingly dominant cause of stroke in women in this age group. Pregnancy and the post-partum period are times of both eager anticipation and increased cerebrovascular risk. Although some of the reasons for an increase in stroke risk over the past decade are not easily explained, one reason for an increase in AIS is a well-known, traditional vascular risk factor — hypertension. The increase in the number of women who suffer a stroke during pregnancy seems to parallel the increased incidence of traditional vascular risk factors appearing in younger women. The effect of elevated blood pressure in pregnant women is particularly virulent, not only immediately during pregnancy and the post-partum period, but extending for years after delivery. Hypertensive disorders of pregnancy have been shown in multiple studies, including this recent one, to be a predictor of future stroke in women. Treatment of hypertension in pregnant women, as well as prior to pregnancy and after delivery, is crucial to decrease stroke risk throughout her lifetime. ■

els including race, vitamin D from food, vitamin D supplements, ultraviolet light-B flux, age, BMI, physical activity, alcohol intake, and hormonal use.

MS was diagnosed in 199 nurses, of which 147 were incident cases diagnosed after the start of the cohort in 1989 and 52 were prevalent cases diagnosed prior to recruitment. The association between maternal exposures to vitamin D and risk of developing MS in the offspring was investigated. Maternal milk intake was inversely associated with the daughters' risk of MS. The risk of MS among the nurse daughters was 38% lower if their mothers consumed 2-3 glasses of milk per day compared to mothers who consumed 3 or fewer glasses of milk per month. The pooled multivariate adjusted RR was 0.62 (95% confidence interval [CI], 0.40-0.95; P trend = 0.001). Mothers' vitamin D intake from food during pregnancy also was inversely associated with the risk of MS in their daughters, with a 40% lower risk when comparing the highest with the lowest quintile of vitamin D consumption. Similarly, predicted 25(OH)D levels in pregnant mothers was inversely associated with the risk of MS in their daughters. Using predicted 25(OH)D as a continuous variable, the pooled adjusted RR was 0.69 (95% CI, 0.56-0.86) for a 10 nmol/L increment.

■ COMMENTARY

This large study with 35,794 nurse mothers and 199 MS cases among their daughters suggests an inverse association between maternal vitamin D exposure and risk of MS in their offspring. If these findings were indeed true, then ensuring a high intake of milk and increasing vitamin D intake and exposure during pregnancy would have a protective effect in lowering the risk of MS in offspring. As the authors acknowledge, there are several limitations to this study. The mothers provided information about their milk intake and diet from about 35-55 years prior to com-

pleting the questionnaire, the serum 25(OH)D levels were not actually measured but were predicted based on several variable factors, and the daughters also already were diagnosed with MS when their mothers were asked to provide the information, raising potential recall bias. The possibility that other ingredients in their diet or other environmental factors influenced the findings cannot be completely excluded as well. However, despite these limitations, the study does raise the possibility of a preventive intervention for a disease that is yet incurable. Further studies are warranted to confirm these findings and to determine the optimal levels of vitamin D exposure for conferring this protective effect. But in the meantime, at least in instances where the risk of MS in the offspring is high because of family history, and especially given the high prevalence of vitamin D deficiency, it might be worthwhile to check the maternal level of vitamin D during pregnancy and bring it up to the current established safe levels. ■

Gabapentin Enacarbil for Sleep Disturbance in Restless Legs Syndrome

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD

Assistant Professor, Neurology and Neuroscience, Weill Cornell Medical College

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

Synopsis: *Gabapentin enacarbil is effective for sleep disturbance in moderate-to-severe primary restless legs syndrome, but frequently causes sleepiness and dizzinesss.*

Source: Winkelman JW, et al. Randomized polysomnography study of gabapentin enacarbil in subjects with restless legs syndrome. *Mov Disord* 2011; doi: 10.1002/mds.23771. [Epub ahead of print]

RESTLESS LEGS SYNDROME (RLS) IS CHARACTERIZED BY IRresistible urges to move to alleviate uncomfortable or painful sensations in the legs. The symptoms are characteristically worse at night and increase with recumbency. RLS can be idiopathic (primary RLS), a side effect of medications (such as antidepressants), or secondary to other conditions (such as pregnancy, renal failure, or a low ferritin level). RLS often is accompanied by periodic limb movements of sleep (PLMS) — involuntary movements that can lead to nocturnal awakenings and associated sleep fragmentation.

In this study, the authors evaluate the safety and efficacy of gabapentin enacarbil, a prodrug of gabapentin, in the treatment of sleep disturbance in RLS. They used a multicenter, randomized, double-blind, placebo-controlled, crossover design with polysomnography to evaluate subjects with moderate-to-severe primary RLS. A total of 136 subjects were randomized, and 114 completed the study. The primary outcome measure was the mean change from baseline in wake time during sleep at weeks 4 and 10; a secondary endpoint was the mean change in frequency of PLMS associated with arousal at these same time points.

Results of the study showed significantly reduced wake time during sleep by 26 minutes ($P < 0.0001$), and a decreased frequency of periodic limb movements with arousal during sleep when compared with placebo. Side effects were common and similar to those of gabapentin; these included dizziness (20% vs 2% with placebo) and somnolence (13% vs 2% with placebo).

■ COMMENTARY

Until recently, the only FDA-approved treatments for RLS were the dopamine agonists ropinirole and pramipexole, both of which can have serious side effects such as impulse control disorders, orthostatic hypotension, and sudden-onset episodes of sleep. Moreover, long-term treatment with these medications can cause drug tolerance, augmentation, and rebound. Accordingly, there has been considerable interest in finding a safer, more effective treatment for RLS and associated sleep disturbance. Gabapentin may afford such benefits, but its usage remains off-label; in contrast, gabapentin enacarbil (Horizant) recently received FDA approval for this indication.

In this study, the authors show that gabapentin enacarbil reduces RLS-associated sleep disturbance. Strengths of the study include the randomized, multicenter, placebo-controlled design, and the use of objective, quantifiable outcome measures. Weaknesses include the short follow-up period, such that the study did not examine potential long-term complications such as augmentation and rebound. In addition, the primary outcome measure — wake time during sleep — does not distinguish between a non-specific sedating effect of the drug vs a specific effect on RLS-associated sleep disturbance. The effect size was also relatively small, and therefore of unclear clinical significance. The dosage used in this study was 1,200 mg daily; it should be noted that the recommended (FDA-approved) dosage is 600 mg/day.

The major question that remains unanswered is whether the short- and long-term efficacy, safety, and tolerability of gabapentin enacarbil are superior to that of other treatments for RLS and associated sleep disturbance. In particular, further studies are warranted to determine whether gabapentin enacarbil has any advantages over immediate-release gabapentin. ■

A Newly Described Motor Neuron Disease Mimic

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: *A new autosomal-dominant genetic disorder is described that has similarities to sporadic motor neuron disease.*

Source: Jokela M, et al. Late-onset lower motor neuronopathy: A new autosomal dominant disorder. *Neurology* 2011;77:334-340.

SPINAL MUSCULAR ATROPHIES (SMA) CONSTITUTE A GROUP OF hereditary degenerative lower motor neuron disorders, the most common and severe of which is SMA Type 1 (Werdnig-Hoffmann disease), presenting in the infantile period, with later-onset, less severe forms including Type 2 (intermediate form) and Type 3 (Kugelberg-Welander disease). Inheritance is autosomal recessive, with nearly all young-onset forms resulting from deletions or mutations in the survival motor neuron 1 (SMN1) gene on chromosome 5q12.2. Adult-onset SMN1 SMA is rare, whereas LMNA mutations, designated as laminopathies, may underlie up to 10% of autosomal dominant (AD) SMA. Two families are now reported with a previously undescribed phenotype of adult-onset, autosomal-dominant SMA, possibly representing a new disorder.

Muscle cramps and fasciculations, with onset in the third decade, were the presenting symptoms among 12 patients in these eastern Finland families. Subsequently, usually after age 50 years, proximal and distal weakness progressed slowly, over decades, in the absence of manifest atrophy, with absent deep tendon reflexes at the knees and ankles. Myalgias, usually in the neck and back but also in the limbs, were reported in six of 12 patients. Upper motor neuron signs were not found, but five had mild pes cavus, three had moderate hammer toes, and one had pes planus, consistent with longstanding neurogenic disease. Only mildly decreased vibratory loss in the feet was seen in five patients, usually asymmetrically, and of two patients with more prominent sensory findings, one had diabetes. All were ambulatory, with only one patient requiring a cane. Coarse hand tremor was demonstrable in four patients, and two experienced drop attack-like episodes. Serum creatine kinase was mildly elevated in all but one, usually two- to three-fold above normal, but did not correlate with disease severity or progression. Needle electromyography revealed neurogenic changes in all limbs in all patients, comprising positive waves, fibrillation potentials, and/or complex repetitive discharges, with motor unit potentials of increased amplitude and duration. Muscle biopsy confirmed this pattern, demonstrating fiber type grouping, group atrophy, nuclear clump fibers, and type II atrophy. Muscle magnetic resonance imaging of the leg muscles revealed diffuse fatty degenerative changes, with the medial gastrocnemius the earliest and most severely affected. Molecular genetic analysis failed to reveal any significant linkage with known motor neuronopathy loci.

■ COMMENTARY

As noted in the accompanying editorial,[1] the classification of spinal muscular atrophies that do not localize to chromosome 5q is quite confusing and this report, if confirmed, will necessarily make it more so. Of importance to the clinician is that this disorder begins with fascicula-

tions, raising the specter of amyotrophic lateral sclerosis (ALS). Weakness, however, is a much-delayed symptom, and atrophy is mild, indicating that this is not typical motor neuron disease. Family history will help, for although 5% of ALS is autosomal-dominant, those patients will not have survived as long as would be expected with this disorder. As always, clinicians beware, and make sure to examine family members when in doubt. ■

Reference

1. Darras BT. Non-5q spinal muscular atrophies: The alphanumeric soup thickens. *Neurology* 2011;77:312-314.

CME Objectives

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

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

CME Instructions

To earn credit for this activity, follow these instructions:

1. Read and study the activity, using the provided references for further research.
2. Log on to www.cmecity.com to take a post-test; tests can be taken after each issue or collectively at the end of the semester. First-time users will have to register on the site using the 8-digit subscriber number printed on their mailing label, invoice or renewal notice.
3. Pass the online tests with a score of 100%; you will be allowed to answer the questions as many times as needed to achieve a score of 100%.
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CME Questions

1. Recent studies of the LRRK2 mutation leading to autosomal dominant inheritance of Parkinson's disease (PD) reveal that:

a. the G2019S mutation has complete penetrance.
b. tremor is uncommon in LRRK2-associated PD.
c. associated non-motor features (such as depression) are rare in LRRK2-associated cases.
d. non-motor features including constipation are more common in non-manifesting LRRK2 carriers than healthy control subjects.
e. G2019S LRRK2 manifests primarily as cognitive dysfunction, with parkinsonism following.

2. Adverse muscle effects during statin usage are more common in:

a. patients who are on statins for > 10 months.
b. diabetics.
c. patients with a history of stroke.
d. patients over 60 years of age.
e. All the above

3. Which of the following statements about vitamin D is *true*?

a. Vitamin D plays an important role in modulating the immune system.
b. People living in temperate climates have a high rate of vitamin D deficiency.
c. Patients with multiple sclerosis and vitamin D deficiency have a higher rate of relapses than those with normal vitamin D serum levels.
d. All of the above are true

4. Which of the following is *true* about gabapentin enacarbil?

a. The most common side effects are sleepiness and dizziness.
b. It reduces restless legs syndrome, but not the associated sleep disturbance.
c. The FDA-approved dosage is 1,200 mg daily.
d. It is the only FDA-approved treatment for RLS.

5. Motor neuron disease (ALS) can be definitively diagnosed in its early stages.

a. True
b. False

6. Which of the following is *true* regarding stroke in pregnancy?

a. The increased caesarian sectioning rate contributed to the increased incidence of stroke associated with pregnancy from 1994-1995 to 2006-2007.
b. Preterm delivery, in women with hypertension during pregnancy, increases risk of future stroke.
c. Cerebral venous thrombosis is rarely associated with pregnancy in the absence of hypertension.
d. Adolescents with hypertension during pregnancy do not have an increased risk of future stroke.

In Future Issues: **Sleep Disorders**

PHARMACOLOGY WATCH

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

ACEIs and ARBs Help Patients with Aortic Stenosis

In this issue: ACEI/ARB therapy for AS; safety alert issued for dronedarone; statins and cancer risk; nesiritide and heart failure; and FDA actions.

ACEI/ARB therapy for aortic stenosis

Drugs that block the renin-angiotensin system are not only safe, they are beneficial in patients with aortic stenosis (AS) according to a new study. This runs counter to current recommendations that suggest that angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) are relatively contraindicated in patients with AS. The study looked at more than 2000 patients with AS in Scotland, of which the majority had mild-to-moderate stenosis, while about one-quarter had severe AS. Of the total number, nearly 700 were on ACEI or ARB therapy. Over a mean follow-up of 4.2 years, just over half the patients died, of which 48% died from cardiovascular (CV) deaths. Those treated with ACEIs or ARBs had a significantly lower mortality rate (adjusted hazard ratio [HR] 0.76; confidence interval [CI] 0.67-0.92; $P < 0.0001$) and fewer CV events (adjusted HR 0.77; 95% CI: 0.65-0.92; $P < 0.0001$) compared to those not on ACEIs/ARBs. The authors conclude that ACEI/ARB therapy is associated with improved survival and lower risk of CV events in patients with AS. These findings were consistent in patients with nonsevere and severe AS. The rate of valve replacement also was lower in patients treated with ACEIs/ARBs (*J Am Coll Cardiol* 2011;58:570-576). This study was a retrospective observational study and prospective, randomized, controlled trials are warranted to confirm these findings. ■

Drug safety alert issued for dronedarone

The antiarrhythmic dronedarone (Multaq) is again coming under scrutiny from the FDA after review of the company-sponsored PALLAS study of more than 3000 patients, which showed that the drug is associated with an increased mortality rate in patients with atrial fibrillation (AF). Dronedarone currently is approved for treatment of paroxysmal AF and atrial flutter. The new study investigated its use in patients with permanent AF. The study was halted early when the mortality rate in the treatment group was found to be double the rate in the placebo group (32 deaths [2%] in the dronedarone arm vs 14 [0.9%] in the placebo arm). The rate of unplanned hospitalization and stroke also was double in the dronedarone group vs the placebo group. All findings were statistically significant. These findings led the FDA to issue a drug safety alert on July 21, 2011. This follows a January 2011 drug safety alert regarding rare but severe liver injury associated with use of dronedarone. Currently, the FDA is recommending that physicians should not prescribe dronedarone to patients with permanent AF while they further evaluate the data (FDA Drug Safety Communication at www.FDA.gov/drugs/drug safety). ■

Statins do not increase risk of cancer

A new retrospective cohort analysis suggests that statins are not associated with an increased risk of cancer. Researchers used the General

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Electric Centricity electronic medical record database of more than 11 million adult Americans to match nearly 46,000 patient pairs by propensity scores receiving and not receiving statin therapy. With an average time in the database of 8 years, the incidence of cancer in patients taking a statin was 11.37% compared with 11.11% in matched patients not taking a statin (HR 1.04; 95% CI: 0.99-1.09). The authors conclude that this analysis demonstrates no statistically significant increase in cancer risk associated with statins, although they do suggest that more research is needed (*J Am Coll Cardiol* 2011;58:530-537). Lingering fears about cancer risk associated with statins was strengthened by the SEAS trial published in 2008, which showed the combination drug simvastatin/ezetimibe (Vytorin) was associated with a two-fold increase in the rate of cancer in a small group of patients. The FDA has continued to study these data along with data from other studies, but this new analysis adds significant evidence of a lack of association between statins and cancer. ■

Nesiritide and heart failure

Nesiritide can no longer be recommended for use in congestive heart failure based on the findings of a new study. The drug is a recombinant B-type naturetic peptide (BNP) that was approved in 2001 for use in patients with acute heart failure. The approval was based on small studies showing a reduction in pulmonary capillary wedge pressure and improvement in dyspnea 3 hours after administration. However, subsequent data raised questions about the drug's safety, especially with regard to worsening renal function and even increased mortality. Based on the recommendations of an independent panel, the manufacturer performed a placebo-controlled randomized trial of more than 7000 patients hospitalized with acute heart failure to assess the drug's safety and efficacy. Patients with heart failure were randomized to receive nesiritide or placebo for 24-168 hours in addition to standard care. The drug was modestly effective at reducing symptoms of dyspnea at 6 and 24 hours. More significantly, however, the rate of rehospitalization for heart failure or death from any cause within 30 days was no different. Nesiritide was not associated with a worsening of renal function but was associated with worsening hypotension. The authors conclude that on the basis of these results, "nesiritide cannot be recommended for routine use in the broad population of patients with acute heart failure" (*N Engl J Med* 2011;365:32-43). ■

FDA actions

The highly anticipated oral factor Xa inhibitor rivaroxaban has been approved by the FDA to reduce the risk of deep venous thrombosis, blood clots, and pulmonary embolism in patients undergoing knee or hip replacement. The once-a-day medication should be taken for 12 days by patients undergoing knee replacement and 35 days for patients undergoing hip replacement. The approval was based on three studies (RECORD 1, 2, and 3) which showed that rivaroxaban is superior to subcutaneous enoxaparin in this role. Bleeding, the primary side effect of the drug, was no more common with rivaroxaban than enoxaparin. Rivaroxaban also has been looked at in phase III trials for stroke prevention in patients with nonvalvular atrial fibrillation, and treatment and secondary prevention of venous thromboembolism, although the FDA has yet to act on approval for these indications. Rivaroxaban was developed by Bayer and is marketed by Janssen Pharmaceuticals as Xarelto.

The FDA has approved ticagrelor, a new antiplatelet drug for patients with acute coronary syndrome, including unstable angina and myocardial infarction (MI). The approval was based on studies that coupled ticagrelor with low-dose aspirin. The approval recommends use with aspirin although it carries a warning that aspirin doses above 100 mg per day may decrease the effectiveness of the drug. Ticagrelor requires twice a day dosing in contrast to the other drugs in this class, clopidogrel and prasugrel, which can be dosed once daily. The approval was based on the PLATO trial, a head-to-head study with clopidogrel which showed that in combination with aspirin, ticagrelor resulted in the lower composite endpoint of cardiovascular death, stroke, or MI (9.8% vs 11.7% with clopidogrel, $P < 0.001$).

The FDA has approved six manufacturers for the 2011-2012 flu vaccine. The strains included this year are A/California7/09 (H1N10), A/Perth/16/2009 (H3N2), and B/Brisbane/60/2008 — the exact same components as last year's vaccine. One of the manufacturers, Sanofi Pasteur, has received permission to market Fluzone Intradermal, the first flu vaccine administered via a novel intradermal microinjection that is touted as being more comfortable than intramuscular injections. The new intradermal system in approved for adults ages 18-64 years. ■

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.*

VOLUME 16, NUMBER 9 PAGES 17-18 SEPTEMBER 2011

Can Appendicitis be Cured with Antibiotics Alone?

Source: Vons C, et al. *Lancet* 2011;377:1573-1579.

SOMETIMES, ACUTE APPENDICITIS (AAP) just goes away. We know this because of abdominal explorations that disclose evidence of chronic appendicitis, indicative of one or more prior episodes. Four randomized trials support the relevance of antibiotic treatment for AAP, but definitive conclusions about the appropriate role of antibiotics in AAP treatment have been limited by aspects of previous study design.

Vons et al performed a controlled trial of adult patients with CT-confirmed uncomplicated AAP who were randomized to antibiotics (amoxicillin/clavulanic acid 3-4 g/d) or surgery. Although one group was assigned to surgery alone, the surgical group also actually received a single parenteral 2 g dose of amoxicillin/clavulanic acid at induction of anesthesia; additionally, if complicated appendicitis was discovered at surgery (i.e., the appendicitis had progressed or was misdiagnosed by CT), antibiotics were subsequently administered even in the surgery group.

Peritonitis within 30 days of intervention — the primary endpoint of the trial — occurred more often in the antibiotic group (8% vs 2%), hence the noninferiority of antibiotic treatment was NOT confirmed. If future tools can do a better job of identifying those who truly have uncomplicated appendicitis, antibiotics may prove to be a more valuable first-line treatment. ■

Antihypertensive Medication Nonadherence and Blood Pressure

Source: Rose AJ, et al. *J Clin Hypertens* 2011;6:416-421.

IT COMES AS NO SURPRISE THAT WHEN PATIENTS do not take their blood pressure (BP) medication, a lapse in BP control is anticipated. On the other hand, when a patient presents with an elevated BP and acknowledges omitted doses, it is difficult to be sure whether the observed elevation in BP is solely due to recent omissions, an underlying worsening of BP (requiring an augmentation rather than just simple restoration of treatment), rebound BP elevation, or some combination of these elements. To gain a more concrete insight into the anticipated impact of omitted BP medication in a typical patient population, Rose et al reviewed data from a population (n = 869) enrolled in a trial investigating the effects of physician communication on BP control. A component of the study design was utilization of medication bottles with memory caps that recorded timing and frequency of opening, providing a detailed view of medication administration.

When comparing BP after a 7-day period of poor adherence (< 60% of prescribed medication administered) to a prior period of excellent adherence, BP was 12/7 mmHg higher immediately following the week of poor adherence.

Clinical inertia — failure to intensify treatment despite suboptimal goal attainment — is sometimes innocently propagated by clinician uncertainty about whether uncontrolled BP should simply be attributed to missed doses or needs treatment augmentation. The authors suggest that clinicians consider a maximum BP excursion of 15/8 mmHg as potentially likely due to poor medication adherence, and that when BP elevation is greater than this amount, consider augmentation of antihypertensive treatment rather than simply encouraging better adherence to the existing regimen. ■

PDE5 Inhibition and Cognitive Function

Source: Shim YS, et al. *Int J Impot Res* 2011;23:109-114.

THE THERAPEUTIC REALM OF PDE5 INhibitors has expanded to include not only erectile dysfunction (ED) but also pulmonary hypertension. Animal studies have identified PDE5 activity in the brain, which can be impacted by currently available PDE5 inhibitors since they readily cross the blood-brain barrier. In the animal CNS, increased cyclic GMP (a pharmacodynamic effect of PDE5 inhibition) is seen in pathways associated with memory; studies have confirmed enhanced cognition in animals with impaired cognition related to diabetes, anticholinergic medications, and hyperammonemia who are treated with PDE5 inhibitors.

Udenafil is a PDE5 inhibitor not available in the United States but already in use in other countries (e.g., Korea, Russia) for treatment of ED. Shim et al undertook a trial of udenafil in men with ED but without known cognitive dysfunction (n = 30). Subjects underwent a battery of tests of cognitive function at baseline and 8 weeks later. Testing metrics included measures of general cognitive function,

verbal learning for episodic memory, and frontal executive function.

Several tests of cognitive function showed statistically significant improvement. Cognitive function improvement was greater in men whose sexual function scores improved the most. The authors suggest further exploration of the effects of PDE5 inhibition on cerebral flow to gain greater understanding of the favorable cognitive effects they have demonstrated. ■

What Things are Making us Gain Weight?

Source: Mozaffarian D, et al. *N Engl J Med* 2011;364:2392-2404.

Since two-thirds of americans are overweight or obese, most of us should probably be trying to better understand why. Perhaps the observation that the daily number of calories per capita continues to increase, while daily energy expenditure dwindles, is enough to satisfy the casual observer. Or is the *character* of caloric intake — such as high glycemic index carbohydrate vs low — a critical factor? As yet, despite simple answers (just reduce calories), there are few simple solutions (folks cannot/will not adhere to calorie-based dietary restrictions).

Might it help to identify commonplace "culprit" foods — that is, dietary components associated most often with weight gain, rather that just total calorie counts?

Based on follow-up of healthy U.S. adults during observational periods lasting as long as 20 years (n = 120,877), Mozaffarian et al determined that several commonplace dietary and lifestyle factors were associated with weight gain. For instance, over a 4-year interval, for every additional daily serving of potato chips, there was a 1.69 lb weight gain. Sugar-sweetened beverages were next on the list of items associated with weight gain. Perhaps, not surprisingly, physical activity, fruits, grains, nuts, and vegetables were inversely associated with weight.

Despite widespread public awareness of the health consequences of being overweight and obesity, most are not able — using currently advised methods — to reverse the trend for weight gain. Whether targeting elimination of specific dietary components (e.g., sugar-sweetened beverages) and/or the augmentation of selected favorable components (e.g., nuts, grains, fruits) will prove to be effective remains to be determined. ■

Clinical Briefs in Primary Care™ is published monthly by AHC Media.

Executive Editor: Leslie Coplin.
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Disease-Modifying Antirheumatic Drugs and Risk for Developing Diabetes

Source: Solomon DH, et al. *JAMA* 2011; 305:2525-2531.

Prior to the advent of disease-modifying antirheumatic drugs (DMARDs), the possibilities for remission of disorders like rheumatoid arthritis (RA) and severe psoriasis (PSOR) were remote. Along with the welcome dramatic clinical improvements seen with DMARDs, concerns about adverse effects — such as adversities associated with either the consequences of their immunomodulatory activity or direct toxic effects — require a high level of vigilance. Recently, however, there has been recognition that biologic DMARDs such as TNF inhibitors or hydroxychloroquine, when used in RA or PSOR, might be associated with a lesser risk of diabetes.

Solomon et al performed a retrospective study of RA/PSOR patients who began treatment with a DMARD (n = 121,280) in the United States and Canada. Compared with nonbiologic DMARDs (examples include sulfasalazine, leflunomide, cyclosporine, and others), use of biologic DMARDs was associated with a 23%-46% lesser risk of new-onset diabetes. Because cardiovascular (CV) risk is magnified in persons with RA, treatment choices may be influenced by consideration of agents less likely to further augment CV risk through induction of diabetes. ■

The Ipswich Touch Test for Diabetic Peripheral Neuropathy

Source: Rayman G, et al. *Diabetes Care* 2011;34:1517-1518.

Type 2 diabetes (dm2) remains the #1 cause of atraumatic limb amputation in the United States. The primary cause of foot ulcers that progress to limb loss is diabetic neuropathy, which decreases sensory awareness of tissue trauma, allowing destruction to progress without warning signs that would otherwise stimulate seeking care for injuries or infections. Albeit consistently recommended by consensus guidelines, routine examination of the feet remains markedly suboptimal by both clinicians and patients alike. Although monofilament and tuning fork testing are highly effective in identifying the presence of diabetic neuropathy, they also remain underutilized.

The Ipswich Touch Test (named after the United Kingdom Hospital in which it was developed) is performed by "lightly touching/resting the tip of the index finger for 1-2 seconds on the tips of the first, third, and fifth toes and the dorsum of the hallux." The presence of neuropathy is defined by this method as having two or more of the eight sites (four sites on each foot) being insensate.

The gold-standard for identification of diabetic neuropathy in this trial was vibration perception threshold as determined by a neurothesiometer. Both monofilament and the Ipswich Touch Test were highly sensitive and had strong positive-predictive value for the presence of neuropathy. When the Ipswich Touch Test compared with monofilament testing, there was near-perfect agreement. As discussed by the authors, perhaps the lack of requirement for specialized measurement tools will prompt clinicians to be more consistently proactive in seeking to define diabetic neuropathy in the feet. ■