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INSIDE

Financial Disclosure:

Neurology Alert's physician editor, Fred Plum, 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.

Telomeres, Dementia, and Mortality

ABSTRACTS & COMMENTARY

By Gregg L. Caporaso, MD, PhD
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Dr. Caporaso reports no financial relationship relevant to this field of study.

Synopsis: *Short telomeres in peripheral white blood cells might be a prognostic marker for dementia and death following stroke, and for Alzheimer's disease and death in the elderly.*

Sources: Martin-Ruiz C, et al. Telomere Length Predicts Poststroke Mortality, Dementia, and Cognitive Decline. *Ann Neurol*. 2006;60:174-180; Honig LS, et al. Shorter Telomeres are Associated with Mortality in Those with APOE Epsilon4 and Dementia. *Ann Neurol*. 2006;60:181-187.

THE ENDS OF EUKARYOTIC CHROMOSOMES ARE CAPPED BY PROtective structures called telomeres. These are composed of long, tandem TTAGGG DNA repeats (10- to 15-kilobase pairs in humans) and associated binding proteins. Evidence suggests that telomeres prevent chromosomal ends from being recognized as broken or damaged DNA and subsequently triggering cellular DNA repair mechanisms. Since conventional DNA polymerases require an RNA primer to initiate DNA synthesis, a portion of 3'-end telomeric DNA of the template strand is not copied, thus resulting in progressive telomere shortening with repeated rounds of cell division. Germ cells, stem cells, and most cancers circumvent this end-replication problem by expressing the enzyme telomerase, a specialized DNA polymerase that can synthesize TTAGGG repeats at 3'-ends. In most somatic cells, which lack telomerase, critical telomere shortening eventually triggers apoptotic cell death or replicative senescence, a permanent exit from the cell cycle. Further, telomere shortening correlates both with cellular aging—which places a limit on proliferative capacity—and with aging of the organism as a whole. Thus, telomeres might serve as a biomarker for aging. Indeed, telomeres in readily accessible peripheral white blood cells have been studied, and telomere length was found to correlate inversely with the prevalence for a variety of age-related diseases, such as atherosclerosis, myocardial infarction, and dementia, as well as death.

VOLUME 25 • NUMBER 1 • SEPTEMBER 2006 • PAGES 1-8

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Two new studies now examine further the possible relationship between telomere length and dementia or mortality. Martin-Ruiz and colleagues prospectively followed a cohort of 195 nondemented survivors of stroke ages 75 years and older. Telomere length in peripheral white blood cells was measured 3 months after the stroke. Subjects were assessed cognitively for the development of dementia for up to 2 years and for survival up to 5 years. Baseline telomere lengths ranged from 4892-7785 base pairs (average 6166 bp). Surprisingly, telomere lengths did not correlate with age. However, there was a significant association between telomere length at baseline and risk of death (a decrease by a factor of 0.49 for every 1000-bp increase in telomere length) or of the development of dementia (odds ratio of 0.19 for every 1000-bp increase). In addition, among subjects with telomere lengths in the shortest quartile, a statistically significant reduction of 1.3 points on the Mini-Mental Status Examination (scale 0-30 points) was seen over 2 years. Martin-Ruiz et al note, though, that most of the risk of death was likewise attributable to the shortest quartile, and that this relationship was weaker and less significant after allowing for MMSE scores.

Using clinical data and stored blood samples from the large Washington Heights-Inwood Columbia Aging Project, Honig and colleagues analyzed relative telomere length, prevalence of Alzheimer's disease (AD), and survival in a case-control study of 257 subjects (mean age 81 years). Subjects were selected from the larger group to provide a study population in which 50% had AD and 50% had died during a 10-year follow-up period. Telomere analysis was performed on blood samples that had been collected upon entrance in the study. Telomere lengths were shorter in those with AD and in those who had died. Subjects who had AD and subsequently died, had the shortest telomeres on average. There was no significant effect of telomere length on mortality in the absence of dementia or in subjects lacking an APOE4 allele but, in subjects with at least one APOE4 allele who fell into the shortest telomere tertile, the odds ratio for mortality was 9 times that of those in the longest tertile after adjustment for dementia status.

COMMENTARY

These 2 studies provide additional evidence supporting a relationship between telomere shortening and age-related diseases or survival. It is difficult to make direct comparisons of their results, though, due to marked differences in their study populations and since the 2 groups used different methods to determine telomere length (Martin-Ruiz et al directly measured telomere length, whereas Honig et al determined the amount of telomeric DNA relative to a marker gene). Nonetheless, this new work complements previous studies that have shown a correlation between short telomeres and either vascular dementia or AD. Further, they add to the existing literature by providing a prospective analysis of telomere length and neurological outcomes and also by showing a relationship between telomere length and mortality in demented, but not nondemented, elderly individuals.

At this time, we may only conjecture about the biological underpinnings of the association between telomere length and dementia or death. Does AD or stroke stimulate an immune response that results in white blood cell proliferation and subsequent telomere shortening? Do neurological diseases evoke other biological responses that actively shorten telomeres independently of cell proliferation, or is telomere loss merely a surrogate measure of telomerase down-regulation? Indeed, a variety of new evidence suggests that telomerase might play a role in cell survival unrelated to telomere extension. Does aging of the immune system, reflected in white blood cell telomere loss, predispose to dementia? The most straightforward explanation, provided by both sets of authors, is that telomere shortening occurs as a result of metabolic stress over an individual's lifespan, which also predisposes to a variety of age-related illnesses. Oxidative stress, in particular, has been linked to atherosclerosis, stroke, and dementia and, more recently, to telomere shortening.[1] One intriguing study found that average telomere

Neurology Alert, ISSN 0741-4234, is published monthly by Thomson American Health Consultants, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/
GROUP PUBLISHER: Brenda Mooney.
EDITORIAL GROUP HEAD: Lee Landenberger.
MANAGING EDITOR: Leslie Hamlin.
GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.

POSTMASTER: Send address changes to *Neurology Alert*, P.O. Box 740059, Atlanta, GA 30374.

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Questions & Comments
Please call **Leslie Hamlin**, Associate Managing Editor, at (404) 262-5416.

length in the peripheral mononuclear blood cells of premenopausal women who perceived psychological stress in their lives was shorter by the equivalent of one decade of aging.[2]

The wide variability seen in telomere lengths within each clinical outcome group, as well as the considerable overlap of telomere lengths between these groups, makes it unlikely that absolute telomere lengths could be used as a prognostic marker for disease outcome or mortality. Both studies used blood samples collected at study entry to determine telomere length. It would be interesting to follow telomere lengths prospectively to see if absolute telomere lengths or rates of telomere shortening have greater prognostic significance. Future studies might also test family members to determine whether short telomeres reflect a genetic predisposition to age-related illnesses that increase susceptibility to death or disease. ■

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1. von Zglinicki T. Oxidative Stress Shortens Telomeres. *Trends Biochem Sci*. 2002;27:339-344.
2. Epel ES, et al. Accelerated Telomere Shortening in Response to Life Stress. *Proc Natl Acad Sci USA*. 2004;101:17312-17315.

Convulsive Status Epilepticus—Clinical Lessons from Epidemiologic Findings

ABSTRACT & COMMENTARY

By Sabiha Merchant, MD

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

Synopsis: *Convulsive status epilepticus is common in children and prognosis is related to the underlying cause of the seizure disorder*

Source: Chin RF; et al. Incidence, Cause, and Short-Term Outcome of Convulsive Status Epilepticus in Childhood: Prospective Population-Based Study. *Lancet*. 2006;368: 222-229.

North London convulsive status epilepticus Surveillance Study Group reported the incidence, cause, and short term outcome of status epilepticus in childhood. They prospectively identified 176 episodes of convulsive status epilepticus (CSE) over a 2-year period from a subset of their 18-hospital network. Important findings from this epidemiological study are the following:

1) The most frequent etiology for CSE in childhood was prolonged febrile seizures.
2) Case fatality for first ever episode of CSE was 3%.
3) Fatality was related to having a pathological cause for CSE, primarily bacterial meningitis and progressive neurodegenerative disorders.
4) CSE related to an acute symptomatic cause occurred frequently in children under one year of age.
5) Among children of all ages presenting with first ever episode of CSE, 56% were previously neurologically healthy with no history of epilepsy and no previous neurological deficits.
6) The short-term recurrence rate for CSE was 13%, with seizures most commonly recurring within 25 days of initial presentation. This short term recurrence rate was similar in both children with previous neurological abnormality and previously health children.
7) Children with a pre-existing neurological abnormality were 2.9 times more likely to have a recurrence after one year from the first episode, compared to previously neurologically normal children.
8) The incidence of CSE in children is higher than that for adult populations.

COMMENTARY

This well executed, prospective study provides useful information regarding the frequency, causes, and mortality of CSE in children. The findings have several implications for clinical management. First, the most common cause of pediatric CSE is a prolonged febrile seizure which is associated with low mortality and morbidity. However, since a major cause of mortality was bacterial meningitis, this study reinforces the need to rule out acute bacterial meningitis in children presenting with CSE and a fever. Timely and vigilant emergent management is important for improving survival for these children.

Since CSE has a high recurrence rate within one year for children with underlying neurological impairments, these findings suggest that this population warrants careful consideration in prescribing antiseizure treatment after the first episode.

Caveats regarding the findings in the study are that the mortality rates may have been underestimated due to the small sample size, and no analysis was made regarding morbidity following CSE. ■

Can Headaches Put the Heart at Risk? Yes, for Patients with Migraine with Aura

ABSTRACTS & COMMENTARY

By Dara G. Jamieson, MD

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

Synopsis: *Active migraine with aura increases risk of myocardial infarction, coronary revascularization, and angina, as well as ischemic stroke. Active migraine without aura and non-migraine headaches are not associated with increased vascular risk.*

Sources: Kurth T, et al. Migraine and Risk of Cardiovascular Disease in Women. *JAMA*. 2006;296:283-291. Erratum in: *JAMA*. 2006;296:332-333, 654; Lipton RB, Bigal ME. Migraine and Cardiovascular Disease. *JAMA*. 2006;296:332-333.

About one in 3 adults have some form of cardiovascular or cerebrovascular disease, and over 28 million Americans have severe and disabling migraine headaches. These common diseases are linked by more than just coincidental overlap. Migraine with aura is associated with an increased risk of ischemic stroke. The relationship between migraine and cardiovascular disease, however, is less well understood. In this report, data from the Women's Heart Study (WHS) was analyzed for correlation between migraine of different types and vascular events.

The WHS was a randomized, placebo controlled trial designed to test the benefits and risks of low-dose aspirin and vitamin E in the primary prevention of cardiovascular disease (CVD) in healthy women. Health care professionals older than 45 years at entry into the study (1992-1994) were randomized to treatment and were followed by questionnaire till the end of March 2004. The primary outcome measurement of this prospective cohort study of women participating in the WHS was the combined endpoint of major CVD (first non-fatal ischemic stroke, first non-fatal myocardial infarct, or death due to ischemic CVD). Of 27,840 women initially free of cardiovascular disease or angina, 18% reported any history of migraine. From the 3610 women with active migraine, 39.7% reported migraine with aura. As compared to women without any migraine history, these women with aura had higher cholesterol and were less likely to drink any alcohol or exercise. They were more likely to use or have used oral contraception or hormone replacement therapy, but they also were less likely to smoke. The women with a prior history of migraine were older (mean age 55.5 years) and had more vascular risk factors than women with active migraine (mean age 53.2 years, with aura; 52.6 years, without aura).

During a mean of 10 years of follow-up there were 251 ischemic strokes, 249 myocardial infarctions, and 130 ischemic CVD deaths in the total cohort. The age and multivariable-adjusted associations between migraine status and vascular events were calculated. Compared with women with no migraine history, women who reported either an active or a prior history of migraine were at increased risk of ischemic events, except for ischemic stroke. The most striking risk was for women with active migraine with aura. After adjusting for age, there were 18 additional major CVD events attributable to migraine with aura per 10,000 women per year. As compared with women with no migraine history, the hazard ratios (HRs) were 2.15 (95% confidence interval, 1.58-2.92; P <.001) for major CVD, 1.91 (95% CI, 1.17-3.10; P =.01) for ischemic stroke, and 2.08 (95% confidence interval, 1.30-3.31; P = .002) for myocardial infarction. Women with migraine with aura also had an increased risk of myocardial revascularization, angina, and CVD death. Increased risk was noted after approximately 6 years of follow-up. Women with active migraine without aura did not have any significantly increased risk of any CVD event or angina compared with women without any migraine history. Women who reported prior migraine had significantly increased risk of coronary revascularization and angina. The highest association between active migraine with aura and ischemic stroke was in women younger than age 50 and women with total cholesterol < 200 mg/dL. In contrast, the association between active migraine with aura and myocardial infarction was not modified by age or cholesterol level. The association between migraine with aura and major CVD, ischemic stroke, and myocardial infarction was not statistically significantly modified by vascular risk factors. No significant association was found between non-migraine headaches and any

CVD events.

COMMENTARY

This study confirms that women with migraine with aura have a greater risk of cardiovascular, as well as cerebrovascular disease. Increased vascular risk remained even after controlling for the increase in risk factors seen in women with migraine with aura. The precise mechanisms to explain the link are currently unknown. Increases in prothrombotic and vasoactive factors are associated with migraine, but other migraine associations, including congenital heart disease, do not correlate with coronary artery disease. The authors of the accompanying editorial (Lipton, et al.) point out that the observations need to be evaluated in men and younger women with migraine. They suggest study of the role of migraine preventative medications or antiplatelet therapy in reducing vascular risk.

Since migraine without aura is far more common than migraine with aura, the majority of migraine patients are not at increased vascular risk. However women who have migraine with aura have increased risk of vascular events, including coronary heart disease and stroke, and should be screened for risk factors. This risk should be considered when counseling patients and selecting drugs for both acute and preventative treatment of migraine headaches.

Does Hemodialysis Cause Dementia?

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Medical College, Cornell University

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

Synopsis: *Moderate-to-severe cognitive impairment is common and under diagnosed in hemodialysis patients.*

Source: Murray AM, et al.Cognitive Impairment in Hemodialysis Patients is Common. *Neurology*. 2006;67: 216-223.

Hemodialysis patients are at increased risk of cognitive dysfunction due to metabolic disturbances, older age, and a high prevalence for cerebrovascular disease, diabetes, and hypertension. In this study, Murray and colleagues utilized neuropsychological testing to systematically measure function across multiple cognitive domains in 374 older hemodialysis patients (mean age = 71.2 years) and 101 age- and sex-matched controls. The controls were free of any chronic renal disease. The prevalence of cognitive impairment in the hemodialysis patients was high, with 73.4% of patients demonstrating moderate to severe cognitive impairment. Of the 13.9% that demonstrated mild impairment, only 12.7% were cognitively normal. Only 2.9% of these patients had any documented history of cognitive impairment. Factors associated with higher frequency of severe cognitive impairment in the hemodialysis cohort included history of stroke, < 8 years of education, and large dialysis volume. When compared to the control group, the hemodialysis group had a significantly higher risk of severe cognitive impairment (odds ratio, 3.54) after adjusting for age, sex, race, education, depression, diabetes, hypertension, and stroke. Murray et al suggest that this degree of cognitive impairment in dialysis patients may impede their ability to comply with dialysis schedules and manage increasingly complex medication regimens for their comorbid illnesses. Murray et al propose that a potential pathophysiological mechanism of cognitive impairment caused by hemodialysis is cerebral ischemia due to hypoperfusion induced by rapid fluid shifts. Two of the features associated with higher risk of cognitive impairment are modifiable—stroke and higher dialysis volume. Murray et al suggest that stroke prevention in dialysis patients should be aggressive.

COMMENTARY

In the 1970s and 1980s there was widespread recognition of a dementing illness occurring in dialysis patients, so-called dialysis dementia or dialysis encephalopathy. Aluminum, the culprit in this condition, was subsequently removed from dialysate, causing the frequency of dialysis dementia to decrease significantly. The general consensus among physicians was that cognitive impairment was no longer a significant problem caused by dialysis. The study by Murray et al calls that notion into serious question. The results suggest that the process of hemodialysis itself may be detrimental to cognitive function, especially in patients with cerebrovascular disease. The main weakness of the study is that it is not clear how much of the cognitive impairment is due to the underlying renal disease, since the control group excluded patients with renal disease. However, the fact that higher dialysis volume was an independent risk factor for severe cognitive dysfunction does, at least, partly implicate the actual

process of hemodialysis. Whether the cause of cognitive impairment is intermittent cerebral hypoperfusion due to fluid shifts, as suggested by Murray et al, is yet to be determined. Future studies prospectively following cognitive function in end-stage renal disease patients who are randomized to start or delay dialysis, would certainly be helpful in further elucidating this matter. Neurologists should be vigilant about screening for cognitive impairment in patients on hemodialysis, and should aggressively treat modifiable cerebrovascular risk factors, as this may protect against severe cognitive impairment.

Teenage Polyneuropathy

ABSTRACT & COMMENTARY

By Michael Rubin, MD

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Dr. Rubin is on the speaker's bureau for Athena Diagnostics, and does research for Pfizer and Merck.

Synopsis: *Most polyneuropathies in teenagers are due to hereditary demyelinating or metabolic disorders.*

Source: Kararizou E, et al. Polyneuropathies in Teenagers: A Clinicopathological Study of 45 Cases. *Neuromuscular Disord*. 2006;16:304-307.

WHAT ARE THE MOST COMMON FORMS OF POLYNEUropathy in teenagers? To address this question, a retrospective review of patients' records ages 13-19 years, referred for nerve biopsy to the Neuropathology Department of Athens University over a 20-year period, was undertaken. Forty-five patients, 32 boys and 13 girls, were included. All had undergone neurological examination, including muscle strength testing, sensory examination, deep tendon reflex evaluation, blood studies encompassing routine biochemistry, hematology, and serology, cerebrospinal fluid analysis, electrodiagnostic studies comprising nerve conduction studies and needle electromyography, and sural nerve biopsy with teased fiber and electron microscopic evaluation. Clinical, electrophysiological, and pathological findings were used to categorize patients into axonal, demyelinating, or mixed axonal and demyelinating polyneuropathy groups.

Based on clinical and electrophysiological data, 38 patients had distal symmetric sensorimotor polyneuropathy, 3 had symmetric sensory polyneuropathy, and 2 each had asymmetric sensorimotor polyneuropathy or mononeuropathy multiplex. Biopsy revealed demyelination in 38 and axonal loss in 7, with endoneurial inflammatory infiltrates in 6 and epineural and perineural infiltrates or positive human polyclonal antibody to C3 and fibrinogen in 2 each. Overall, 28 patients (62.2%) were diagnosed with hereditary neuropathy, encompassing hereditary motor and sensory (Charcot-Marie-Tooth) type-I (n = 11, 24.4% overall), type-II (n = 6, 13.3% overall), and type-III (n = 2, 0.04% overall), Friedreich ataxia (n = 6, 13.3% overall), hereditary neuropathy with liability to pressure palsy, Roussy-Levy syndrome, or hereditary sensory neuropathy type-I (1 each, 0.02% overall). Nine (20%) demonstrated chronic inflammatory demyelinating polyneuropathy (CIDP), 4 (8.8%) suffered from a hereditary metabolic disorder, including metachromatic leukodystrophy, adrenoleukodystrophy, porphyria, or Fabry disease, and 2 each (4.4%) had toxic or vasculitic neuropathy. As opposed to adults, but similar to children, hereditary neuropathy comprises a large proportion of teenager polyneuropathy. CIDP is twice as common in teenagers, as compared to children, but other causes have a similar incidence throughout the first 2 decades of life.

COMMENTARY

Nerve biopsy can assist in the identification of teenage and childhood polyneuropathy. Yet, electrophysiologic studies remain the cornerstone of evaluation, providing a rational approach to timely and correct diagnosis. Among 74 children with polyneuropathy, nerve conduction studies categorized patients into 5 groups (Polat M, et al. *Pediatr Neurol*. 2006;35;11-17). Acute, axonal polyneuropathy was seen in 32 (43%), chronic axonal polyneuropathy in 16 (22%), demyelinating motor and sensory polyneuropathy in 13 (17%), pure sensory polyneuropathy in 11 (15%), and high-low syndrome (a newly defined electrodiagnostic pattern with peripheral nerves relatively unresponsive even to stimuli of long duration and high voltage, motor amplitudes low, prolonged latencies, slowed motor velocities, absent sensory responses, and normal needle electromyography) in 2 (3%). Precise etiologic diagnosis was possible in all children with acute axonal polyneuropathy, pure sensory polyneuropathy, and high-low syndrome. No etiology was found in 5 (31%) chronic axonal and 3 (23%) demyelinating motor and sensory polyneuropathy cases. Diabetes was the most common cause (n = 9, 82%) of pure sensory polyneuropathy. Toxic neuropathy comprised 56% (n = 18) of acute axonal polyneuropathy, caused by vincristine (n = 9), glue sniffing (n =

7) or organophosphate poisoning (n = 2). Nerve conduction studies and EMG should be considered an extension of the physical examination, and will prove cost-effective when performed as part of the evaluation of children with polyneuropathy. ■

Restless Legs Syndrome: A Disorder of Dopamine Neurotransmission

ABSTRACT & COMMENTARY

By Melissa Nirenberg, MD

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

Synopsis: *PET scans using 2 different dopamine receptor ligands demonstrate abnormalities in dopaminergic transmission in subjects with restless legs syndrome, in the striatum and in extra-striatal regions including thalamus and anterior cingulate cortex.*

Source: Cervenka S, et al. Support for Dopaminergic Hypoactivity in Restless Legs Syndrome: A PET Study on D2-Receptor Binding. *Brain*. 2006;129:2017-2028.

This case-control study examined 16 subjects with restless legs syndrome (RLS) and 16 age-matched control subjects. RLS subjects' mean age was 55 ± 7 years, and none had taken mediations for RLS. One had occasionally taken zolpidem for insomnia. Symptom duration was 27 ± 12 years, and 9/16 had a family history of RLS. Positron emission tomography (PET) data were obtained using the dopamine receptor ligands [11C] raclopride, in addition to [11C] FLB 457, which has sufficiently high dopamine D2 receptor affinity to allow analysis of regions outside the striatum, ie, where receptor density is low. Data obtained during evening hours revealed higher [11C] raclopride striatal binding potential (BP) in RLS subjects compared with controls (2.79 ± 0.22 vs 2.61 ± 0.17, $P = 0.029$). [11C] FLB 457 BP was higher in RLS subjects compared with controls in the thalamus (right medial and left posterior sub-regions), left insula, and rostral anterior cingulate cortex. A subgroup of 8 subjects and 8 matched controls were also examined in the morning. As in the evening, [11C] raclopride BP was higher in cases than controls, but neither regional nor sub-regional analysis of [11C] FLB 457 demonstrated statistically significant extra-striatal differences. There was no significant difference in PET data obtained in the morning compared with evening, despite documented differences in subjects' symptoms as expected from diurnal changes in RLS.

COMMENTARY

RLS is a common neurological disorder affecting up to 10% of the population. It responds to treatment with dopaminergic agents, but the reasons for such a response, and its precise anatomic substrates, remain unclear. The present study re-investigates the controversial question of whether there exist dopamine neurotransmission abnormalities in RLS and, in contrast to previous investigations, finds increased striatal dopamine receptor BP. Prior studies have been conflicting, with reduced striatal dopamine receptor ligand binding in 2 studies, and normal BP in 2 studies. However, previous findings have been criticized due to timing of scans (RLS symptoms peak at night, and scans are routinely performed earlier in the day), and for lack of adequate controls for medication use and other variables. Cervenka and colleagues have directly addressed these concerns, and although a full explanation for differences in published results remains unclear, the present study has a number of advantages in its methodology that make its results compelling.

A further advantage of the present study is that it is the first use of [11C] FLB 457 in RLS, which allows measurements of dopamine binding outside of the striatum. In identifying involvement of sub-regions of the thalamus and anterior cingulate cortex, Cervenka et al suggest an explanation for the effect of dopaminergic agents upon the sensory symptoms and urge to move that are so disturbing to RLS patients. Finally, what do BP differences detected in RLS mean? As Cervenka et al point out, altered BP may result from a change in available receptor density or, less likely, a change in ligand binding affinity. Increased [11C] raclopride or [11C] FLB 457 BP, therefore, may reflect: 1) decreased intrasynaptic dopamine, or 2) increased dopamine receptor number, which could possibly be due to receptor hypostimulation. Intriguingly, receptor number is affected by dopamine agonist or antagonist exposure, as well as by opioid receptor agonists. This study, therefore, supports, although it does not directly demonstrate, dopaminergic hypoactivity in RLS. More importantly, it provides a springboard for further studies aimed at improving, understanding, and treatment of this common and debilitating condition. ■

CME Questions

10. The association between short telomeres in peripheral white blood cells and dementia most likely represents:
a. a direct effect of telomere shortening on dementia.
b. the influence of biological aging (reflected by short telomeres) on susceptibility to dementia.
c. an effect of dementia on telomeres.
d. the effects of single-gene mutations.

11. Women who have migraine with aura:
a. have a similar risk of myocardial infarct to that of women without migraine aura.
b. have an increased ischemic stroke risk with increased age.
c. have an increased risk of ischemic stroke and myocardial infarction, even corrected for vascular risk factors.
d. do not have increased vascular risk when the data was age-adjusted.
e. do not have an increased risk of angina.

12. Choose the *correct* statement:
a. CIDP is twice as common in teenagers as compared to children.
b. Hereditary neuropathy is rare in children.
c. Nerve biopsy plays little or no role in the diagnosis of neuropathy in children
d. Choices 1-3 are all true
e. Choices 1-3 are all false

13. Which of the following factors is independently associated with increased risk of severe cognitive impairment in hemodialysis patients?
a. Cerebrovascular disease
b. Coronary artery disease
c. Greater than 12 years of education
d. Presence of diabetes
e. Presence of hypertension

14. Which of the following statements concerning PET studies in RLS is *true*?
a. Abnormal dopamine neurotransmission is limited to the striatum.
b. Results are likely to be unaffected by prior medication exposure.
c. PET studies demonstrate significant diurnal variation in dopamine receptor binding potential abnormalities.
d. Abnormal dopamine neurotransmission occurs in the thalamus and anterior cingulate cortex.
e. PET data recorded early in the day fail to demonstrate abnormalities in dopaminergic neurotransmission.

Answers: 10. (b); 11. (c); 12. (a); 13. (a); 14. (d)

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The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs; and

• To discuss nonclinical issues of importance to neurologist, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

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Raloxifene's Role for Estrogen- and Age-Related Problems

What is the role of raloxifene for the treatment of osteoporosis and breast cancer prevention? Raloxifene is a selective estrogen-receptor modulator similar to tamoxifen. There has been considerable interest in the drug in the role of treatment for osteoporosis and, perhaps, breast cancer prevention, especially in light of the Women's Health Initiative findings on conjugated estrogen/progesterone. A new study does little to clarify the issue, however, suggesting, like previous studies, that raloxifene has benefits, but also significant risks associated with its use.

As part of the Raloxifene Use for The Heart (RUTH) trial, more than 10,000 postmenopausal women with CHD or multiple risk factors for CHD were randomized to raloxifene 60 mg daily or placebo and followed for a median of 5.6 years. The 2 primary outcomes were coronary events and the rate of breast cancer. Raloxifene had no effect on the risk of primary coronary events (533 vs 553 events; HR, 0.95; 95% CI, 0.84 -1.07) but was associated with a reduced risk of invasive breast cancer (40 vs 70 events; HR, 0.56; 95% CI, 0.38-0.83). However, the all-cause death rate was the same in both groups, and raloxifene use was associated with an increased rate of fatal stroke (59 vs 39 events; HR, 1.49; 95% CI, 1.00-2.24) and venous thromboembolism (103 vs 71 events; HR 1.44: 95% CI, 1.06-1.95). The drug was associated with a reduced risk of clinical vertebral fractures (64 vs. 97 events: HR, 0.65; 95% CI, 0.47-0.89) (*N Engl J Med*. 2006;355:125-137). In an accompanying editorial, Marcia L. Stefanik, PhD, from the Stanford University Medical School reviews risk benefit profiles of raloxifene for women.

Reviewing data from the RUTH trial, as well as other studies, the author suggests that a key issue in contemplating raloxifene use is balancing the benefits of reduction in the risk of breast cancer and vertebral fractures with the increase risk of venous thromboembolism and fatal stroke. She suggests that raloxifene should be contemplated in women with an increased risk of breast cancer, but asks" What level of breast cancer risk would justify the use of raloxifene for prevention of breast cancer for a given person . . ." and suggest that the answer to that question is currently unknown. She also states that, "For now, there's no magic bullet that can reduce the risks of major health problems related to estrogens and aging without introducing other potentially serious health concerns." (*N Engl J Med*. 2006;355:190-192).

The Truth About Multivitamins

More than half of the adult population in the United States takes multivitamins on a regular basis, yet little is known about the benefits or lack of benefits of vitamins. The National Institutes of Health has published a "State-of-the-Science Conference Statement" on multivitamin/mineral

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supplements and chronic disease prevention as an early release article on the *Annals of Internal Medicine* web site on August 1. The statement deals with the current patterns of vitamin use, nutrient intake of vitamin users and nonusers, the efficacy of single vitamins and minerals, the efficacy of multivitamins, the safety of multivitamins, and where future research is needed. Regarding single vitamins and minerals, the results have been disappointing.

Beta-carotene was found to cause an increase in lung cancer incidence and deaths in smokers and male asbestos workers and no benefit in preventing other types of cancers. Other cancer preventative studies have shown no benefit from beta-carotene and, some have even suggested, increase rate of stroke and CVD in women smokers. Vitamin A has not been the subject of individual trials but, when paired with beta-carotene or zinc, there is no impact on the incidence of cancer.

Four trials have looked at vitamin E, and the results have been mixed. The largest was the Women's Health Study, which suggested a decrease rate of cardiovascular deaths with vitamin E but no decrease in the incidence of CVD events. Vitamin B_6 was looked at, and 2 small studies showed no benefit regarding cognitive decline in elderly men and women. Folic acid with or without vitamin B_{12} has been shown to decrease the rate of neural tube defects in women of childbearing age, but was not shown to prevent cognitive decline in older adults. Selenium was found to decrease the rate of liver cancer in Chinese patients who were at risk, and there may be some benefit in reducing the rate of lung, prostate, and colorectal cancer. Calcium has been shown to increase bone mineral density in post menopausal women, and calcium coupled with vitamin D has been shown to decrease the risk for hip and non-vertebral fractures. Calcium and vitamin D may increase risk of kidney stones, and has not been shown to reduce the risk of colorectal cancer.

The use of multivitamins and mineral supplementation (MVM) has been studied in 5 randomized, controlled trials. Although the study methodology was quite variable, there is a suggestion that MVM may decrease risk of cancer. No studies have shown any benefit as far as cardiovascular disease, and the benefit for cataract prevention is mixed. Progression of macular degeneration may be slowed by certain multivitamins, and may represent the single most important benefit from multivitamins. The conference statement also stated that the FDA should be given more oversight over the vitamin industry, and that more rigorous randomized controlled studies should be done of individual vitamins, minerals, and MVM, including safety of these products, as well as the interactions with nutrients and medications (www.annals.org 1 August 2006, to be published in print 5 September 2006).

Statins and Hepatitis C

Statins may be effective therapy for hepatitis C infections, and may even be used in combination with interferon to inhibit replication of the hepatitis C virus, according to new study. Japanese researchers recently evaluated the effect of various statins with or without interferon on hepatitis C replication. The synthetic statin fluvastatin was the strongest inhibitor of HCV replication, while atorvastatin and simvastatin were less effective. Lovastatin's effect was relatively weak, while pravastatin displayed no anti-HCV activity. The authors suggest that statins, especially fluvastatin, could be "potentially useful as new anti-HCV reagents" in combination with interferon (*Hepatology*. 2006;44:117-125).

Preventing Hot Flashes

Gabapentin may be as effective as estrogen in preventing hot flashes in postmenopausal women, based upon a recent study. In a randomized, double-blind, placebo-controlled trial on 60 postmenopausal women randomized to conjugated estrogen 0.625 mg daily, gabapentin titrated to 2400 mg daily, or placebo for 12 weeks. The primary outcome, the hot flash composite score, was no different between estrogen or gabapentin (72% improvement vs 71%), with placebo reducing symptoms by 54%. No differences were seen in severity of hot flashes or depression symptoms, although side effects were slightly higher in the gabapentin group (*Obstet Gynecol*. 2006;108:41-48). The authors acknowledge that this is a small study with a significant placebo effect. However, in light of the Women's Health Initiative findings, non-estrogen alternatives for heart flashes are welcome.

FDA News

The FDA is opening the door to allow Duramed's Plan B emergency contraceptive to be available over-the-counter to women 18 and older. Previously the FDA had tabled the OTC application indefinitely, but new FDA leadership is more receptive. The drug is currently available only by prescription. ■