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INSIDE

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Status Epilepticus in Cancer Patients: Does It Make a Difference If the Tumor is a Primary Brain Tumor or Systemic Metastasis?

ABSTRACT & COMMENTARY

By Adilia M. Hormigo, MD, and Cynthia L. Harden, MD

Drs. Hormigo and Harden report no financial relationships relevant to this field of study. Dr. Hormigo works at the Memorial Sloan-Kettering Cancer Center. Dr. Harden works at the Comprehensive Epilepsy Center.

Synopsis: *Status epilepticus, in the setting of cancer, is treatable and does not appear to increase mortality above the risk of the underlying disease.*

Source: Cavaliere R, et al. Clinical Implications of Status Epilepticus in Patients with Neoplasms. *Arch Neurol*. 2006;63:1746-1749

STATUS EPILEPTICUS (SE) IS DEFINED AS A SERIES OF RECURRENT grand mal seizures without return of consciousness between them, or persistent seizure activity for at least 30 minutes. Although the standard definition for SE requires 30 minutes of seizure activity, the need for rapid intervention and early treatment has led to a consideration of impending status with a shorter duration of continuous seizure activity.[1] SE is a neurological emergency and stepwise treatment is implemented to control this potentially fatal condition. Patients with brain tumors or intracranial metastases, either in the brain parenchyma or leptomeninges, are at increased risk for developing seizures, and subsequently SE.

This study by Cavaliere, et al analyzed factors that may lead to SE and affect prognosis in the cancer population. Over a period of 8 years, the authors found 35 patients (25 with primary brain tumors) at the University of Virginia who developed SE secondary to the tumor or its treatment. Twenty of those patients (57%) were

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taking anti-convulsant drugs when they developed SE, and 11 (55%) had subtherapeutic levels. Approximately one quarter of this small cohort developed SE in one of the following 3 settings, determined by brain imaging: 1) at the time of tumor diagnosis, 2) with tumor progression, 3) with stable tumor. The remaining fraction had either tumor regression or insufficient imaging to determine the status of the tumor.

Eight patients (23%) died within 30 days of SE; 5 had systemic cancer and other contributing factors for a seizure disorder, including infections, strokes, intraparenchymal hemorrhage or metabolic imbalance. Half of the subjects with systemic tumors died within 30 days of status epilepticus, in contrast to only 12% of subjects with primary brain tumors. Half of the SE occurrences consisted of generalized tonic-clonic (GTC) seizures, and was the seizure type in most of the subjects who died within 30 days.

Although details are not provided about specific treatment regimens, SE was successfully treated in most patients with benzodiazepines and phenytoin. Three patients required additional phenobarbital, one received propofol, and one required a medically induced coma.

COMMENTARY

This is a retrospective study that looked at the incidence, contributing and prognostic factors for SE among patients with primary or metastatic tumors to the brain and meninges and their treatment. The mortality rate was similar to what has been reported for other causes of SE, and overall survival correlated with the expected survival for the underlying tumor. Patients with systemic cancer had a higher risk of death in the 30-day period after SE; these patients were also older and had other concurrent illnesses. No statistically significance correlation was seen between 30-day mortality after SE and age, seizure type, tumor status, prior seizure disorder, or need for endotracheal intubation.

An important lesson emerges from this study. If a patient has had a seizure and is on AEDs, it is important to keep the dose in a therapeutic range since low AED levels (55% of patients on AEDs) appear to be one modifiable risk factor for developing SE in this population. Secondly, partial SE and any type of SE in patients with primary brain tumors is associated with less risk of death in the short term and therefore, good response to adequate treatment can be expected in this group. Unfortunately, there is no information about the duration of SE or management algorithms. The use of fewer than 3 drugs to control SE suggests that SE in the cancer population is amenable to treatment and efforts should be made to determine the optimal pharmacologic regimen. ■

Reference:

1. Chen JW, Wasterlain CG. Status Epilepticus: Pathophysiology and Management in Adults. *Lancet Neurol.* 2006;2:246-256.

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Neonatal MRI as Predictor of Neurodevelopmental Outcome in Preterm Infants

ABSTRACT & COMMENTARY

By Barry Kosofsky, MD, PhD
Professor of Pediatrics and Neurology, and Chief of Pediatric Neurology at Weill Cornell Medical Center
Dr. Kosofsky reports no financial relationships relevant to this field of study.

Synopsis: *This article reports a strong correlation between abnormal MRI at term equivalent in preterm infants with adverse neurodevelopmental outcomes at 2 years of age, suggesting its utility for risk stratification.*

Source: Woodward LJ, et al. Neonatal MRI to Predict Neurodevelopmental Outcomes in Preterm Infants. *N Engl J Med.* 2006; 355:685-694.

Very preterm infants born before 32 weeks have significant rates of neurodevelopmental disabilities ranging from neurosensory impairments and learning disabilities to cerebral palsy (CP).

Known risk factors for neurodevelopmental adverse outcomes include sepsis, surgery, postnatal use of steroids, bronchopulmonary dysplasia, intraventricular hemorrhage, and periventricular leukomalacia. MRIs on these newborns show a variety of white matter and some gray matter abnormalities.

This prospective longitudinal study reports an association between gray and white matter abnormalities on MRI at term equivalent and neurodevelopmental outcomes defined by a battery of standardized tests at age 2. It also compares MRI to existing prognostic indicators. The subjects included 167 very preterm infants enrolled at 2 different institutions, all born at 30 weeks of gestation or less. MRIs were performed at term equivalent using 1.5 Tesla magnets. Scans were categorized using a standardized scoring system developed during this study, consisting of five 3-point scales for white matter abnormalities (signal abnormalities, volume loss in periventricular area, cystic abnormalities, ventricular dilatation, callosal thinning) and three 3-point scales for gray matter abnormalities (signal abnormalities, quality of gyral maturation, size of subarachnoid space). Cranial ultrasounds were performed during the first 2 days and at 4-6 weeks of life. At 2 years of age, these children were assessed clinically, and identified as having severe cognitive delay, severe motor delay, CP, or neurosensory impairment based on scoring on standardized tests like the Bayley scale and the Mental Development Index, as well as examination by a pediatric neurologist.

This study found poorer performance on the cognitive and psychomotor scales and increased risk of severe cognitive delay, severe motor delay, CP and severe neurosensory impairment with increasing severity of white matter abnormalities. Children with gray matter abnormalities also fared similarly except there was no significant association with neurosensory impairment. The study found the presence of moderate-to-severe white matter abnormalities to independently correlate with adverse neurodevelopmental outcome more strongly than known predictors. In particular, MRI identified patterns of brain injury were demonstrated to be more sensitive and specific than cranial ultrasonography. Postnatal use of corticosteroids remained a significant predictor of adverse outcomes after adjusting for MRI abnormalities and other known risk factors.

Of note, a substantial proportion of infants with moderate-to-severe white matter abnormalities were free of severe impairment at 2 years of age thus indicating the potential protective role of other genetic and environmental factors.

COMMENTARY

This study demonstrates the superiority of MRI over cranial ultrasound to predict neurodevelopmental outcome of very low-birth-weight preterm infants, which is probably a result of both the superior spatial resolution as well as the increased sensitivity of MR to detect neuronal and axonal damage. The additional cost and reduced access to MRI may make it a less attractive option for routine screenings, particularly for serial assessments during the early postnatal period when cranial ultrasonography can assess 4 out of 5 parameters for white matter abnormalities that authors measured on MRI. However, the added sensitivity and specificity of MRI warrants its use, particularly when performed at 40 weeks post-conception, to utilize the positive and negative predictive value demonstrated in this report, which will be of tremendous help for practicing neonatologists and child neurologists to assist with the prognosis and care of this population of infants at significant risk for developmental disabilities.

Prognostic Predictors in ALS

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, NewYork Presbyterian Hospital, Cornell Campus

Dr. Rubin reports no financial relationship to this field of study.

Synopsis: *Faster progression of ALS is predicted by older age, presentation with bulbar signs, or presentation with distal limb muscle weakness.*

Source: Czaplinski A, et al. Predictability of Disease Progression in Amyotrophic Lateral Sclerosis. *Muscle Nerve.* 2006;34:702-708.

Among 1034 patients seen between 1984-2004 and registered in the amyotrophic lateral sclerosis (ALS) database at Methodist Neurological Institute, Houston, 832 with definite or probable ALS had undergone at least 2 Appel ALS (AALS) evaluations and were included in this study, undertaken to define predictors of disease progression,

which was defined as a 20-point change in the AALS score. AALS score measures muscle strength, and arm, leg, bulbar, and respiratory function, with scores ranging from 30 (normal) to 164 (maximal dysfunction). Data collected and evaluated encompassed clinical, laboratory, and electromyographic results from the initial visit, subsequent significant interventions including percutaneous endoscopic gastrostomy (PEG), noninvasive ventilation (NIV), and tracheostomy, and tri-monthly quantitative disease progression evaluations using the AALS score and forced vital capacity (FVC). Statistical analysis included Kaplan-Meier, log-rank, and Cox model 1 and 2 tests.

Men comprised 69.3% (n = 570) and women 30.7% (n = 253) of the 832 patients included in this study. Average age of onset was 53.3 years, with bulbar onset experienced in 16.4% (n = 135). Initial examination was delayed on average 15.9 months from symptom onset. 27.3 % (n = 225) and 12.4% (n = 102) of patients underwent, or were placed on PEG or NIV, respectively. 41.9% (n = 345) were prescribed riluzole 50 mg twice daily, in most instances at the initial evaluation. Median time to 20-point AALS disease progression was 9 months, and was observed in 70.8% (n = 583). Slower deterioration significantly correlated with age under 40 years, male gender, and limb as opposed to bulbar onset. No prognostic difference was appreciated between arm or leg onset in the limb-onset group, but patients with proximal limb involvement trended toward slower progression compared to those with distal limb involvement. AALS score less than 60 at initial evaluation, slower rate of progression between first symptom and first examination, and longer time between first symptom and first examination were all significantly associated with slower progression. The latter clinical features, as well as age and site of symptom onset, are all independent covariates of ALS progression.

COMMENTARY

Effective therapy remains the pot-of-gold at the end of the rainbow in amyotrophic lateral sclerosis (ALS) research. Transgenic SOD G93A mice have recently been reported to demonstrate later disease onset when given erythropoietin, a known inhibitor of neurodegenerative processes, including those resulting from hypoxia, inflammation, excitotoxic injury, and oxidative stress (Grunfeld JF, et al. *Exp Neurol.* 2006, doi:10.1016/j.expneuol.2006.11.002). Survival was not affected and, surprisingly, only females benefited, raising doubt as to whether this finding is real, considering that no pathophysiologic gender difference is known to exist in ALS. Translating this into a tangible benefit for humans seems unlikely. Further research into ALS therapeutics remains most welcome. ■

Low Vitamin D Levels May Increase Risk of Developing MS

ABSTRACT & COMMENTARY

By Brian R. Apatoff, MD, PhD
Associate Professor of Neurology and Neuroscience;
Director, Multiple Sclerosis Clinical Care and Research Center
Dr. Apatoff reports no financial relationship relevant to this field of study.

Synopsis: *Vitamin D supplementation may lower the risk of developing multiple sclerosis.*

Source: Munger KL, et al. Serum 25-Hydroxyvitamin D Levels and Risk of Multiple Sclerosis. *JAMA*. 2006; 296:2832-2838.

The investigators performed a prospective, case-control study of more than 7 million U.S. military personnel who had serum samples stored in the Department of Defense Serum Repository. Multiple sclerosis (MS) cases were identified through military disability databases from 1992 to 2004, and the diagnosis of definite or probable MS was confirmed by independent review of the medical records. Each established case of MS (n = 257) was matched to 2 control cases by age, sex, race/ethnicity, and dates of blood testing. Vitamin D status was determined by averaging 25-hydroxyvitamin D levels in 2 or more serum samples collected prior to the onset of initial MS symptoms.

Among the white military personnel diagnosed with MS (n = 148; 296 controls), the risk of developing MS was significantly decreased with increasing levels of 25-hydroxyvitamin D. Among whites, there was a 41% decrease in MS risk for every 50 nmol/L increase in 25-hydroxyvitamin D (odds ratio 0.59; 95% confidence interval 0.36-0.97; $P = 0.04$). There was no significant difference between male and female groups. In analysis by quintiles, MS risk was highest in the individuals in the bottom quintile, and risk for MS was lowest among those in the top quintile of 25-hydroxyvitamin D levels. The overall association between MS risk and 25-hydroxyvitamin D levels was not statistically significant among blacks and Hispanics, but none of the black patients or their controls had high levels of vitamin D.

COMMENTARY

The incidence of MS worldwide is higher in northern

latitudes and lower in the equatorial regions. In addition to recognized genetic and environmental/infectious factors, one protective variable of southern climates might be increased vitamin D production from sunlight exposure. Previous epidemiological analyses of large nursing databases from the Harvard School of Public Health have demonstrated that women whose vitamin D intake was approximately 400 IU/day had a 40% lower risk of developing MS than women who did not take supplements (*Neurology Alert.* 2004).

Vitamin D is also commonly added to multivitamins and combined with calcium, usually for postmenopausal women at increased risk for osteoporosis. While the current study does suggest a preventative role for vitamin D in reducing the risk of acquiring MS, it does not address whether vitamin D supplements can alter the course of existing MS. Since first degree family members of persons with MS have approximately a 20-fold increased risk of developing MS, is it reasonable for this "at-risk" group to be take vitamin D supplements?

In general, MS patients may have reduced sun and UV light exposure because of avoidance of heat. They may also be at higher risk of osteopenia from treatment with corticosteroids and a more sedentary lifestyle. It is reasonable to have patients on a vitamin D supplement for this health benefit alone. More study is needed of the immune mechanisms of MS and the immunomodulatory effects of vitamin D, before we can make broader recommendations regarding vitamin D supplementation. ■

Dystonia and the Long Distance Runner

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

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Dr. Henchcliffe reports no financial relationship to this field of study.

Synopsis: *This case series describes clinical features and treatment responses of an unusual focal leg action dystonia in 5 long distance runners.*

Source: Wu LJ and Jankovic J. Runner's Dystonia. *J Neurol Sci*. 2006;251:73-76.

The authors describe 5 unusual cases of focal leg and/or foot dystonia occurring in long distance runners seen at an academic movement disorders center. Mean age at symptom onset was 37.4 ± 10.33 years (range 20-46 years), and mean symptom duration at the time of evaluation was 7.2 ± 4.44 years (range 2-12 years). Three of the 5 subjects were women. Four of the 5 had foot flexion or inversion as a presenting symptom, and in 3 of these it spread to involve knee extension, with hip flexion in one. In one subject, only the distal limb was involved. In all cases, symptoms were initially present only when running, and triggers later identified included walking on tip toes, squatting, cycling > 20 minutes, walking up stairs, and running wearing shoes. Three found sensory tricks to relieve dystonia, including walking backwards, walking on heels, and touching the hip. Two subjects exhibited a dystonic tremor with typical null point, that is, relief with certain postures. Only 2 of the cases are described in detail, and both had a prior injury, superficial to both knees after tripping in one (2 months prior to symptoms), and knee injury with swelling from a motor vehicle accident followed by patellar tendon transfer (10 months prior to symptoms) in the other. In all 5 cases, brain MRIs and EMG/NCV studies were normal, there was no family history of dystonia, and DYT1 gene testing was negative in the 3 cases in which it was performed. Patients responded to botulinum toxin A injections (n = 2), levodopa (n = 1), carbamazepine (n = 1), trihexiphenidyl (n = 1), but no details are available as to how many other medications were tried in each case.

COMMENTARY

Focal adult-onset dystonias most commonly involve blepharospasm, torticollis, and oromandibular dystonia. Isolated adult-onset foot dystonia is often a red flag that the patient will go on to develop Parkinson's disease or another parkinsonian disorder. However, the unusual pattern of dystonia described here, with an isolated limb presentation, and association with voluntary motor activity, fits with other focal action dystonias such as writer's cramp, musician's dystonia,[1] and (likely) golfers' "yips." Moreover, the authors have adequate time periods of follow up without parkinsonian symptoms developing. Such disorders can be challenging to recognize, leading to misdiagnosis in some; of note, one of the above cases was seen by 2 neurologists, a psychiatrist, and 3 orthopedic surgeons prior to diagnosis. In particular, the paroxysmal nature of the movements, and somewhat bizarre phenomenon of sensory tricks, can lead to the impression of a psychogenic disorder. The range of treatments used

successfully by the authors is encouraging, but there is clearly much to learn. In particular, the authors caution that if mistaken for an orthopedic disorder, casting could be recommended, and this could be detrimental based upon case reports of dystonia onset after limb immobilization. However, there are also reports of treatment of limb dystonia involving immobilization. Finally, as the authors point out, a prior history of limb injury in 2/5 cases raises the question of whether these could be peripherally induced movement disorders. Overall, this small case series highlights a fascinating and poorly understood disorder, and will hopefully enhance its recognition in other individuals, as well as stimulate further study. ■

Reference:

1. Frucht SJ. Focal Task-Specific Dystonia in Musicians. *Adv Neurol.* 2004;94:225-230.

Lipoprotein(a) and Ischemic Stroke Risk: Who is At Risk?

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

Associate Professor of Clinical Neurology, Weill Medical College

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

Synopsis: *Lipoprotein(a) is a low density lipoprotein that is implicated in atherosclerotic cerebrovascular disease. Elevated levels of Lp(a) appear to confer an increased risk of ischemic stroke. However, its variability in different populations leads to uncertainty about the utility of routine screening.*

Sources: Ohira T, et al. Lipoprotein(a) and Incident Ischemic Stroke: The Atherosclerosis Risk in Communities (ARIC) Study. *Stroke*. 2006;37:1407-1412.
Rigal M, et al. Lipoprotein (a) and Risk of Ischemic Stroke in Young Adults. *J Neurol Sci.* 2007;252:39-44.

LP(A) IS A LOW DENSITY LIPOPROTEIN, FOUND IN human plasma, which consists of apolipoprotein(a) covalently linked to apolipoprotein B-100. It differs from low density lipoprotein cholesterol (LDL-C) by the apo(a) component, which has a marked size heterogeneity. Its role in the promotion of vascular disease, including ischemic stroke, has been investigated based on several putative mechanisms. Gene expression of the unique glycoprotein apo(a) has been found in atherosclerotic intracerebral and carotid vessels and may presage the development of atherosclerotic plaque in cerebral vessels. The structural homology between apo(a) and plasminogen indicates a role for Lp(a) in the inhibition of tissue plasminogen and thus it may interfere with intrinsic fibrinolysis. Lp(a) is involved in endothelial dysfunction and in the induction of inflammation.

Despite pathophysiological explanations, study of the correlation between elevated levels of Lp(a) and ischemic stroke in specific populations has yielded variable results. The clinical relevance of elevated levels of Lp(a) may be gender, race, and age specific. For example, Lp(a) levels are higher in African-Americans than in whites, and in women than in men. The effect of elevated levels of Lp(a) may depend on the vascular bed with greater cardiovascular, than cerebrovascular, relevance. Specific assays and serum sample storage issues may also factor into the results of clinical investigation. Relevance has varied according to clinical trial design with correlation more likely in case-control and cross-sectional studies, than in prospective population studies. Trials have variably distinguished between ischemic and hemorrhagic stroke end-points.

Two large prospective studies found somewhat disparate risk results based on gender differences. A study by Ariyo et al, published in 2003, found that among older adults in the United States, an elevated level of Lp(a) was an independent predictor of stroke and vascular death in men, but not in women.[1] They were not able to explain the absence of an association between Lp(a) and risk of vascular events in women, despite higher levels of Lp(a) in women in their population. In an analysis of the Women's Health Study data, published by Suk Danik et al in 2006, very high levels of Lp(a) in initially healthy women, aged 45 years and older, were predictive of future cardiovascular events, especially in association with elevated levels of LDL-C.[2]

In the paper by Ohira et al 221 men an d women, aged 45 to 64 years at initiation, participated in the ARIC Study from 1987 and 1989. They were followed for an average of 13.5 years to determine the incidence of stroke through 2002. The Lp(a) level was a single determination at initiation into the

study. Qualifying strokes, extracted from hospital records, were classified as to hemorrhagic or ischemic, and type of ischemic stroke was determined when possible. Adjusted geometric mean values of Lp(a) were higher in blacks than whites ($P < 0.001$), and women than men ($P < 0.001$). LDL-C levels were greater with increasing Lp(a) levels. Kaplan-Meier plots of ischemic stroke according to Lp(a) levels, stratified by race and gender, showed a significant difference by Lp(a) level in black women (log-rank test, $P = 0.03$) and white women ($P = 0.0005$), but not in black men ($P = 0.69$) and white men ($P = 0.90$). There was no dose-response relationship between Lp(a) levels and ischemic stroke incidence, indicating a threshold response. Exclusion of cardioem-bolic strokes increased the association between Lp(a) levels and ischemic stroke incidence in men, reaching statistical significance in black men. The study concluded that a high level of Lp(a) is associated with an increased incidence of ischemic stroke in blacks and white women, but not in white men. The authors pointed out that in prior prospective studies assessing stroke incidence, stroke type and race have not been factored into the interpretation of results. Timing of the measurement of the sample as well as the assay of the specific apo(a) isoform also impacts trial results.

The large prospective population studies have examined the risk associated with Lp(a) in an older population, but less is known about younger stroke patients. Rigal, et al studied the impact of Lp(a) on the risk of ischemic stroke in young adults. They collected data on 100 patients (42 women; 58 men) with acute ischemic stroke, aged 18 to 55 years, who were evaluated as neurological inpatients in Toulouse, France, between 2003 and 2005. One hundred controls, free of vascular disease, were matched for gender and age. Vascular risk factors, but not race/ethnicity, were recorded. Smoking, significantly more common in male patients, was associated with a higher ischemic stroke risk. Multivariate logistic regression analysis, adjusting for risk factors, found that higher levels of Lp(a) were significantly associated with ischemic stroke in men, but not in women. The Lp(a) levels did not correlate with the ischemic stroke type by TOAST criteria. The risk of ischemic stroke was significantly elevated with slightly elevated concentrations of Lp(a) and was not further increased with higher levels of Lp(a), indicating a threshold effect.

COMMENTARY

The known involvement of Lp(a) in multiple mechanisms of atherosclerotic cerebrovascular disease should point toward its designation as a significant risk factor for ischemic stroke. However, the studies of its clinical relevance continue to show variable results. Elevated levels seen in African-Americans and women do not necessarily correlate with reproducibly increased risk in these populations. There seems to be a threshold effect with increasing elevations not necessarily increasing risk, except maybe in women. At this point, with the uncertainty about its relevance and the difficulty with its assay, routine screening for elevated Lp(a) levels does not appear practical. Intervention to decrease elevated levels of Lp(a) is not more specific than management of elevated LDL-C levels, with which Lp(a) appears to be correlated. Further studies are needed to show how elevated Lp(a) levels should explicitly dictate patient management.

References:

1. Ariyo AA, et al. for the Cardiovascular Health Study Investigators. Lp(a) Lipoprotein, Vascular Disease, and Mortality in the Elderly. *New Engl J Med*. 2003;349:2108-2115
2. Suk Danik J, et al. Lipoprotein(a), Measured With an Assay Independent of Apolipoprotein(a) Isoform Size, and Risk of Future Cardiovascular Events Among Initially Healthy Women. *JAMA*. 2006;296:1363-1370.

CME Questions

11. Which of the following is true?

a) Mortality correlates with the duration of SE in cancer patients.
b) Patients with primary brain tumors and SE have a higher 30-day mortality
c) SE in cancer patients can be controlled with benzodiazepines and phenytoin.
d) 30 day mortality correlated with seizure type.
e) A patient is in SE when the duration of seizure activity is at least an hour.

12. Independent covariates of ALS progression include

a. Age
b. Site of symptom onset
c. AALS score less than 60 at initial evaluation
d. Slower rate of progression between first symptom and first examination
e All the above

13. Which of the following statements is true?

a. The incidence of multiple sclerosis is uniform throughout the world.
b. Low vitamin D levels are associated with progressive MS.
c. First-degree family members of MS patients have a 20-fold increased risk of developing the disease.
d. Menopause and osteopenia exacerbate multiple sclerosis.

14. Which of the following statements applies to adult-onset focal action dystonias?

a. They do not respond to medication.
b. They typically become generalized.
c. They usually affect those over 65 years.
d. They may respond to botulinum toxin injections.
e. They are seldom disabling.

15. Which of the following statements best describes our knowledge of Lp(a):

a. Increased Lp(a) levels appear to correlate with increased levels of LDL-C.
b. Lp(a) has been shown to be a significant risk factor for ischemic stroke in young women.
c. Levels of Lp(a) are independent of race/ethnicity.
d. Screening for Lp(a) levels will impact patient management.
e. Men have higher levels of Lp(a) than women.

Answers: 11.(c) 12.(e) 13. (c) 14. d) 15.(a)

CME Objectives

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;

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

Corrections

Please note the following corrections. We apologize for any confusion or difficulty these mistakes may have caused.

1. In last month's issue of *Neurology Alert*, the article entitled "FDDNP PET in Mild Cognitive Impairment" was mistakenly attributed to Dr. Brian Apatoff. It was written by Dr. Norman Relkin.

2. Also in last month's issue of *Neurology Alert*, the article entitled "Is Long-term Use of the Ketogenic Diet Safe and Effective?" was mistakenly attributed to Dr. John C. Caronna. It was written by Dr. Sabina Merchant.

In Future Issues:

Risk Stratification for TIAs

PHARMACOLOGY WATCH

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

Higher HDL Cholesterol in Statin Therapy, Key to Slowing Atherosclerosis?

Aggressive statin therapy is associated with slowed progression and even regression of atherosclerosis. A new study suggests that, when monitoring statin therapy, increases in HDL cholesterol may be as important as decreases in LDL cholesterol in preventing disease progression. Researchers from the Cleveland Clinic reviewed 4 large studies from United States, North America, Europe and Australia in which 1,455 patients with angiographic coronary disease underwent serial intravascular ultrasonography while receiving aggressive statin therapy for 18 or 24 months. During therapy, mean LDL levels dropped from 124.0 mg/dl to 87.5 mg/dl, and mean HDL levels increased from 42.5 mg/dl to 45.1 mg/dl, and LDL to HDL ratios were reduced from a mean of 3 to 2.1 ($P < 0.001$ for all). These changes were accompanied by a small, but statistically significant decrease in atheroma volume as measured by intravascular ultrasound. The largest decrease in atheroma volume was associated with patients with LDL cholesterol less than the mean of 87.5 mg/dl, and percentage increases in HDL cholesterol of greater than 7.5%. The authors conclude that when treating with statins, decreases of LDL cholesterol and increases in HDL cholesterol are independently associated with regression of atheroma volume. They also note that these changes were not associated with reductions in clinical events or improved clinical outcomes and that more research is needed (*JAMA*. 2007; 297:499-508).

Citalopram Useful for Depression in CDA Patients

Major depression affects up to one quarter of patients hospitalized with coronary artery disease and these patients have a worse prognosis than non-depressed patients. A new study from Canada compares the efficacy of citalopram vs interpersonal psychotherapy in reducing depressive symptoms among these patients. The study randomized 284 patients with CAD and major depression to 12 weeks of interpersonal psychotherapy plus clinical management vs clinical management only, and a second randomization compared 12 weeks of citalopram 20-40 mg/day vs placebo. The main outcomes were scores on objective depression scales. Citalopram was superior to placebo in reducing depression scores ($P = 0.005$), but interpersonal psychotherapy was ineffective, being no better than clinical management. The authors conclude that citalopram administered in conjunction with weekly clinical management was effective in treating depression whereas there was no evidence of value for interpersonal psychotherapy. The authors suggest that citalopram or sertraline (based on previous studies) should be considered as first-step treatment for patients with CAD and major depression (*JAMA*. 2007;297:367-379). An accompanying editorial agrees that citalopram and sertraline are safe and effective for treatment of depression in patients with coronary heart disease, and suggests physicians should actively screen for signs and symptoms of depression in these patients. However, there is not yet

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5431. E-mail: jennifer.corbett@ahcmedia.com.

any evidence that treating depression in this patient population reduces subsequent cardiac events (*JAMA*. 2007;297:411-412).

When to Stop Anticoagulation Before Surgery?

For patients on warfarin who have been bridging therapy with low molecular weight heparin (LMWH) prior to surgery, when is the best time to stop anticoagulation? A new study suggests that the evening before surgery is too late. Researchers in Ontario, Canada, looked at 80 patients who were scheduled for surgery or invasive procedures and were bridged with LMWH. All 20 patients had normal renal function and were given enoxaparin 1 mg/kg of body weight twice daily with the last dose administered the evening before surgery. Blood anti-factor Xa heparin levels were measured shortly before surgery, an average of 14 hours after the last dose. Two-thirds of patients had anti-Xa heparin levels of 0.5 U/ml or higher shortly before their invasive procedure. Patients with higher BMIs were more likely to have higher levels as were patients with lower creatinine clearances. The authors conclude that preoperative bridging with twice daily enoxaparin results in high residual anti-Xa heparin levels if the last dose is given the evening before surgery. They recommend that the last dose be given the morning on the day prior to surgery (*Ann Int Med.* 2007;146:184-187).

Drug Warnings: Ranibizumab and Bevacizumab

Both of Genentech's anti-angiogenic agents, ranibizumab (Lucentis) and bevacizumab (Avastin), have been the subject of new warnings from the company and the FDA. Ranibizumab, which is used for the treatment of neovascular (wet) macular degeneration, has been associated with increased risk of stroke in elderly patients. The drug, which is administered as an monthly intraocular injection, was found to be associated with a 1.2% risk of stroke at the recommended dose of 0.5 mg compared to a 0.3% risk associated with the lower-than-recommended 0.3 mg dose ($P = 0.02$) at an average follow-up of 230 days. Patients who had a history of stroke were at the highest risk. Bevacizumab, which is approved for treatment of non-small cell lung cancer and metastatic colorectal cancer, was recently found to be associated with increased risk of gastrointestinal perforation and potentially fatal pulmonary hemorrhage. Gastrointestinal perforation was seen as a complication of patients treated for colorectal cancer, while pulmonary hemorrhage was seen in patients receiving chemotherapy plus bevacizumab for lung cancer. Other bleeding complications seen in bevacizumab-treated patients including GI hemorrhage, subarachnoid hemorrhage and hemorrhagic stroke.

Growth Hormone Treatment, More Harm Than Good

The January 16, 2007, *Annals of Internal Medicine* includes a review of the safety and efficacy of growth hormone in the healthy elderly. The review was undertaken because growth hormone is widely recommended and sold as an anti-aging agent in this population. The authors reviewed 31 articles, which included a total of 220 participants who received growth hormone. The mean age was 69 and patients were generally overweight. Treatment duration mean was 27 weeks. Growth-hormone-treated patients compared to placebo- treated patients were noted to have decreases in overall fat mass and increases in overall lean body mass, but weight did not change significantly. Total cholesterol decreased, although not significantly, after adjustment for body composition changes. Bone density and other lipid levels did not change. Those treated with growth hormone were significantly more likely to experience soft tissue edema, and arthralgias, carpal tunnel syndrome, and gynecomastia as well as a slightly increased rate of diabetes and impaired fasting glucose. The authors conclude that growth hormone use in the elderly is associated with small changes in body composition and an increased rate of adverse events and cannot be recommended (*Ann Int Med*. 2007; 146:104-115).

FDA Actions

The FDA has warned against unsupervised use of topical anesthetic products for cosmetic procedures. The agency has received multiple reports of adverse events associated with patients applying excess amounts of topical agents containing lidocaine, tetracaine, benzocaine, and prilocaine. Two women who used topical anesthetics with lidocaine and tetracaine died after applying the creams to their legs and wrapping their legs in plastic to increase absorption. Healthcare professionals are cautioned to prescribe topical anesthetics with caution in the lowest concentration consistent with pain relief goals and to advise patients in their safe use.

The FDA has approved Roche's orlistat for over-the-counter use to facilitate weight loss. The drug, available in prescription form under the trade name "Xenical," blocks absorption of fat by inhibiting pancreatic lipase thus preventing triglyceride absorption in the small bowel. The over-the-counter version will be available as a 60 mg dose, half the prescription dosage. Orlistat over-the-counter will be marketed as "Alli." ■