Providing Evidence-based Clinical Information for 22 Years

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

Thomson American Health Consultants Home Page—www.ahcpub.com

CME for Physicians—www.cmeweb.com

THOMSON
AMERICAN HEALTH CONSULTANTS

INSIDE

Further Evidence that Mitochondrial Dysfunction May Play a Critical Role With Migraine Pathogenesis

ABSTRACT & COMMENTARY

Synopsis: *CoQ10 significantly reduced the number of days with migraine attacks and significantly reduced in the number of days with nausea.*

Source: Sandor PS, et al. Efficacy of Coenzyme Q10 in Migraine Prophylaxis: A Randomized, Controlled Trial. *Neurology*. 2005;64:713-715.

THERE IS A SUBSTANTIAL BODY OF EVIDENCE, USING 31 phosphorous NMR spectroscopy, that there are abnormalities in brain energy metabolism in migraine. This has been reported by at least 2 or 3 investigators. In addition, elevation of cerebral lactate has also been reported in migraine during the inter-ictal period. Further evidence in favor of the potential role of mitochondrial dysfunction in migraine is the observation that patients with MELAS syndrome have increased migraine headaches. This is caused by a mitochondrial transfer-RNA leucine mutation. In a previous controlled clinical trial, riboflavin produced a significant beneficial effect in preventing migraine headaches (Schoenen, et al. 1998).

In the present trial, Sandor and colleagues carried out a double-blind, controlled clinical trial of coenzyme Q10 (CoQ10) for migraine prophylaxis. They examined CoQ10 administered as 100 mg 3 times a day, as compared to placebo in 42 migraine patients. Patients were examined with placebo for a 1-month baseline. On the second visit, they were randomized to CoQ10 or placebo if they had at least 1 migraine attack in the preceding month. The primary outcome variable was change in attack frequency by month 4, as compared with baseline. Secondary outcome variables included reduction in migraine days, mean headache duration per day, mean severity per day, and days with nausea and vomiting. Sandor et al observed that CoQ10 significantly reduced the number of days with migraine attacks. This became apparent at the 1, 2, and 3 month after time points. This was a significant effect. In addition, the 50%

VOLUME 24 • NUMBER 8 • APRIL 2005 • PAGES 57-64

NOW AVAILABLE ONLINE
www.ahcpub.com

responder rate for headache frequency was higher in patients treated with CoQ10 than with placebo. The response rate was 47.6% for CoQ10 treated patients, as compared to 14.4% for placebo. This rate in the placebo group is comparable to that previously observed in other clinical trials. Sandor et al also found that there was a significant reduction in the number of days with nausea in the patients treated with CoQ10.

COMMENTARY

As noted above, there is substantial evidence that there may be links between mitochondrial dysfunction and migraine headaches. Mitochondrial dysfunction may result in increased membrane excitability, which could lead to spreading cortical depolarization response. The spreading cortical depolarization of Leão has been linked to migraine aura. One would expect that it might be more readily activated in patients who had reduced membrane potential due to mitochondrial defects.

This is the second control trial which shows that administration of agents, which can improve mitochondrial function, may have activity in preventing migraine headaches. This is certainly an area which needs further investigation. Administration of CoQ10 is associated with virtually no side effects of the doses utilized in the present study. Similarly, riboflavin treatment is relatively benign. This, therefore, might lead to a new treatment for migraines, which would be relatively free of side effects. CoQ10 is an excellent candidate for children or women of child bearing age due to its excellent tolerability. — **M. FLINT BEAL**

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: Robert Kimball.
ASSOCIATE 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.

Back issues: $42. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

THOMSON AMERICAN HEALTH CONSULTANTS™

Subscriber Information

Customer Service: 1-800-688-2421
Customer Service E-Mail Address:
customerservice@thomson.com
Editorial E-Mail Address: leslie.hamlin@thomson.com
World-Wide Web: www.ahcpub.com

Subscription Prices

United States
1 year *with* free AMA Category 1 credits: $319
Student/Resident rate: $125
Multiple Copies
Documents are available for multiple subscriptions. For pricing information, please call Steve Vance at (404) 262-5511.
Canada
Add 7% GST and $30 shipping.
Elsewhere
Add $30 shipping.

Accreditation

Thomson American Health Consultants (AHC) designates this educational activity for a maximum of 25 hours in category 1 credit toward the AMA Physician's Recognition Award. Each physician should claim only those hours of credit that he/she actually spent in the educational activity.

AHC is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide CME for physicians.This CME activity was planned and produced in accordance with the ACCME Essentials.

This CME activity is intended for the neurologist. It is in effect for 36 months from the date of the publication.

Questions & Comments

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

Statement of Financial Disclosure

In order to reveal any potential bias in this publication, and in accordance with Accreditation Council for Continuing Medical Education guidelines, we disclose that Dr. Apatoff is on the speaker's bureau of Biogen and Teva. Dr. Relkin is on the speaker's bureau of Pfizer, Eisai, and Athena Diagnostics and does research for Pfizer and Merck. Dr. Rubin does research for ASTA Medica and Eli Lilly. Dr. Beal is a consultant for Mitokor and Avicena. Dr. Segal is on the speaker's bureau of Boehringer-Ingelheim. Dr. Plum, Dr. Frucht, Dr. Lado, Dr. Reich, and Dr. Trifiletti report no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.

Thomson American Health Consultants accepts pharmaceutical sponsorship of some programs but only in the form of unrestricted educational grants that must meet all ACCME and ANCC requirements.

Food for Thought

ABSTRACT & COMMENTARY

Synopsis: *NG feeding should be used for dysphagic patients early and PEG feeding reserved for those who do not tolerate NG feeding or who require long-term tube feeding.*

Source: Dennis MS, et al. Routine Oral Nutritional Supplementation for Stroke Patients in Hospital (FOOD): A Multicenter, Randomized, Controlled Trial. *Lancet*. 2005;365:755-763; Dennis MS, et al. Effect of Timing and Method of Enteral Tube Feeding for Dysphagic Stroke Patients (FOOD): A Multicenter, Randomized, Controlled Trial. *Lancet.* 2005;365:764-772.

NUTRITIONAL SUPPORT IS AN INTEGRAL PART OF the management of neurologically ill patients. The FOOD trials were designed to assess the effect of feeding on outcome in adult stroke patients. In the first FOOD trial, 125 hospitals in 15 countries enrolled more than 4000 stroke patients. Those patients who could swallow were randomly assigned to a normal hospital diet or a normal hospital diet plus nutritional supplements equivalent to 360ml at 6.3 kJ/ml and 62.5 g/L in protein every day until hospital discharge. The primary outcome was death or poor outcome at 6 months after stroke.

Of the 2016 patients allocated to receive supplements, 79 (4%) did not receive any due to staff error, patients refusal, or clinical worsening. An additional 540 patients (28%) stopped receiving supplements before discharge, mainly because of patient refusal. The reasons for refusal were not liking the taste, unwanted weight gain, or feelings of nausea. The mean duration of hospital stay in the supplemented groups was 34 days. There was no significant difference between groups for any complications. Pneumonia and urinary tract infection were the most common in-hospital complications (6% and 7%, respectively).

The study did not show a significant effect of

routine, oral nutritional supplements on the 6-month outcome of acute stroke patients, a not surprising result given that only 8% of enrolled patients were considered to be undernourished at baseline. Therefore, the study could not exclude a potential benefit from nutritional supplements in undernourished stroke patients.

The second report (pages 764-772) describes 2 food trials that included stroke patients unable to swallow. The first of these latter trials studied the effect of the timing of early feeding on post stroke outcome: Patients enrolled within the first week of admission were randomly allocated to early tube feeding via percutaneous endoscopic gastrostomy (PEG) or nasogastic (NG) feeding, or to no tube feeding for more than 7 days. In the other trial, the route of administration of early tube feeding was studied. Patients were allocated to PEG or NG feeding and primary outcome assessed at 6 months.

In the early (less than a week) vs late (after a week) tube feeding trial, almost 900 patients were enrolled by 83 hospitals. There was no significant difference in outcome between early tube feeding and late, although there was an absolute reduction in mortality of 5.8% that was not significant (P = 0.09). There was no excess of pneumonia associated with tube feeding. The rate of gastrointestinal (GI) hemorrhage was higher with early tube feeding rather than late (22 vs 11, P = 0.04). The trend favoring improved survival in the early tube feeding group was offset by an almost 5% increase in survivors with a poor outcome. Dennis and colleagues speculate that early tube feeding kept patients alive who would have otherwise died, but their improved survival was in a severely disabled state.

In the PEG vs NG tube trial, 321 patients were enrolled in 47 hospitals in 11 countries. PEG feeding was associated with a 1% absolute increase in risk of death that was not significant and a 7.8% increase in risk of death or poor outcome that was significant (P = 0.05). GI hemorrhage was more frequent with NG, rather than PEG tube feeding (18 vs 5, P = 0.005). Therefore, Dennis et al recommend that NG feeding should be used for dysphagic patients early and PEG feeding reserved for those who do not tolerate NG feeding or who require long-term tube feeding.

COMMENTARY

The 3 FOOD trials provide useful information on how and when to provide nutrition in acute stroke patients. The first trial found that oral food supplements are not necessary for patients who are not malnourished. The second observed that early tube feeding did not reduce stroke disability, and may have promoted the survival of severely disabled patients. The third study reported that NG tube feeding was superior to PEG tube feeding in the first weeks after stroke. Others have observed contradictory results. For example, Norton and colleagues (*BMJ.* 1996;312:13-16), in a small series of 30 patients, reported that PEG tube feeding, compared to NG tube feeding, significantly reduced mortality and aspiration pneumonia after stroke. The experience of clinicians is that NG tube feeding is more troublesome, if not more dangerous, than PEG tube feeding because NG tubes are subject to misplacement and obstructions; can produce ulceration of the nasal mucosa and reflux esophagitis, and allow aspiration of stomach contents. Nevertheless, the FOOD trial results underscore the need for clinicians to carefully consider the risks and benefits of the 2 routes of enteral nutrition in the first weeks after the onset of an acute stroke. — **JOHN J. CARONNA**

Is it MS or Neuromyelitis Optica? A New Diagnostic Assay

ABSTRACT & COMMENTARY

Synopsis: *NMO-IgG immunofluorescence staining for an additional 14 patients with multifocal neurologic findings were initially suspected to be paraneoplastic disorder.*

Source: Lennon VA, et al. A Serum Autoantibody Marker of Neuromyelitis Optica: Distinction From Multiple Sclerosis. *Lancet.* 2004;364:2106-2112.

LENNON AND COLLEAGUES AT THE MAYO CLINIC tested serum from 102 North American patients with neuromyeltis optica (NMO) and 12 Japanese patients with optic-spinal multiple sclerosis with an indirect immunofluorescence assay, using a composite substrate of mouse tissues that identified a distinctive NMO-IgG staining pattern. Control serum samples were also tested from more conventional multiple sclerosis (MS) patients and other neurological disease. With their assay methodology, the NMO-IgG staining localized to

the blood-brain barrier, outlining central nervous system (CNS) microvessels, pia, subpia, and Virchow-Robin space, and partly co-localizing with laminin. The sensitivity of the serum assay was 73% (95%; CI, 60-86), and specificity was 91% (CI, 79-100%) for NMO. For the Japanese variant of optic-spinal MS, the sensitivity of the serum assay was 58% (95%; CI, 30-86), and specificity was 100% (CI, 66-100%). Some of the patients appeared to have high antibody titers in the thousands, although a relatively low titer of 1:60 was the considered to be positive. Lennon et al further established NMO-IgG immunofluorescence staining for an additional 14 patients with multifocal neurologic findings that were initially suspected to be paraneoplastic disorder.

COMMENTARY

Neuromyelitis optica (Devic's syndrome) is a severe idiopathic inflammatory demyelinating pathology that preferentially affects the optic nerves, often bilaterally, and the spinal cord, usually with extensive lesions spanning multiple vertebral segments. There is usually an absence of clinical brain involvement, and brain MRIs lack the typical periventricular demyelinating lesions seen with MS. The cerebrospinal fluid may demonstrate inflammatory cells in NMO, but usually lacks increased parameters of IgG synthesis or oligoclonal IgG banding. It has been reported that NMO may respond better to corticosteroids and cytotoxic immunosuppressive agents than the immunomodulatory treatments interferon-beta or glatiramer acetate used in MS.

It is surprising that Lennon et al selected only 22 patients with classical MS as controls. No information is given as to how these few MS serum samples were presumably, randomly selected. It would have been reasonable to include at least as many MS patients as NMO patients, particularly patients presenting with clinically isolated syndromes of severe optic neuritis or transverse myelitis. If this assay can be validated and reproduced in other laboratories, then it may have helpful diagnostic and therapeutic implications. For example, patients with NMO IgG staining might be more effectively treated with interventions directed at an IgG that is presumably pathogenic for this inflammatory pathology. This might include corticosteroids, cyclophosphamide, plasmapheresis, rituxamab, or IgG-absorption methods. By more precisely defining the antigen specificity of the NMO-IgG in the CNS, we can hope to have a more complete understanding of this unique neuroimmunological disorder. — **BRIAN R. APATOFF**

Risk Factors for the Development of Diabetic Neuropathy

ABSTRACT & COMMENTARY

Synopsis: *Cardiovascular risk factors are significantly associated with the development of diabetic neuropathy and modification of these parameters should be aggressively encouraged as part of the management of diabetic neuropathy.*

Source: Tesfaye S, et al. Vascular Risk Factors and Diabetic Neuropathy. *N Engl J Med.* 2005;352;341-350.

WHAT, APART FROM TIGHT GLYCEMIC CONTROL, might a diabetic undertake to reduce the risk of developing diabetic neuropathy? Among diabetics participating in the 31 center European Diabetes Prospective Complications Trial (EURODIAB, which ran from 1989-99), neuropathy and its possible risk factors were assessed at baseline and at follow-up, a mean 7.3 years later. All patients underwent clinical examination, quantitative sensory, autonomic function testing (change in heart rate and systolic blood pressure on standing after a 5-minute rest), measurement of serum lipid, lipoprotein, and glycosylated hemoglobin, and assessment of urinary albumin excretion rate from a single 24-hour urine collection. Cardiovascular disease was defined on the basis of previous myocardial infarction, angina, bypass surgery, stroke, or ischemic changes on electrocardiogram. Symptoms of neuropathy were present for 6 months, and patients with alternative causes of neuropathy, besides diabetes, were excluded. Diagnosis of neuropathy was based on the presence of 2 or more neuropathic symptoms, absent ankle or knee deep tendon reflexes, abnormal vibration perception threshold, and abnormal autonomic function (postural hypotension or loss of heart rate variability). Student's t-test, the Mann-Whitney U test, and logistic-regression models provided statistical analysis.

Of 3250 patients enrolled in the trial (1668 men and 1582 women, mean age 32.7 years, mean disease duration 14.7 years), 1819 were without neuropathy at baseline. Of these, 647 were lost to follow-up and, of the remaining 1172, 276 (23.5%) developed neuropathy by study completion. After adjusting for duration of diabetes and glycosylated hemoglobin levels, risk factors significantly associated with development of diabetic neuropathy included total cholesterol ($P = 0.001$), LDL cholesterol ($P = 0.02$), triglycerides body-mass index, hypertension, smoking history ($P < 0.001$ for all 4 factors), as well as retinopathy, albuminuria, von Willebrand factor level, and history of cardiovascular disease. Cardiovascular risk factors are significantly associated with the development of diabetic neuropathy, and modification of these parameters, should be aggressively encouraged as part of the management of diabetic neuropathy.

COMMENTARY

In the United States, diabetes affects more than 6% of the population and, as a result of its complications, accounts for the most common cause of adult blindness (diabetic retinopathy) and renal failure. More than 50% of diabetics will develop neuropathy and, in turn, the most common cause of non-traumatic amputations (Feldman E. *J Clin Invest.* 2003;111;431-433). Four pathways of glucose metabolism have been implicated in the pathogenesis of diabetic neuropathy. Increased polyol pathway activity results in over-production of sorbitol and fructose, depletes cellular anti-oxidant capacity and, ultimately, alters signal transduction. Glucose may become oxidized, forming advanced glycation end-products, which activate receptors and interfere with intracellular protein function. Glycolytic intermediates may activate PKC and result in oxidative stress, inflammation, and increased vascular disease, which may also result from enhanced hexosamine pathway activity, escape of fructose-6-phosphate, and reactive oxygen species generation, which impairs axonal transport and gene expression. Despite the pathway diversity, commonality exists as each is perturbed by glucose excess and consequent superoxide surplus generated by the mitochondrial transport chain. Neuronal and Schwann cell apoptosis, depressed levels of nerve growth factor, neurotrophin-3, ciliary neurotrophic factors, and insulin growth factor are the end result, and these findings correlate with the development of neuropathy. — **MICHAEL RUBIN**

Acetyl Carnitine Works for Diabetic Neuropathy

ABSTRACT & COMMENTARY

Synopsis: *Painful diabetic neuropathy appears to respond to 1000 mg t.i.d. of ALC, but larger, longer trials, initiated early in the course of diabetic neuropathy, are warranted to confirm these results.*

Source: Sima AAF, et al. Acetyl-L-carnitine Improves Pain, Nerve Regeneration, and Vibratory Perception in Patients With Chronic Diabetic Neuropathy. Diabetes Care. 2005; 28:96-101.

TWO MULTICENTER, DOUBLE-BLIND, PLACEBO-controlled, year-long trials were undertaken to assess the efficacy and safety of acetyl-L-carnitine (ALC), 500 or 1000 mg thrice daily (t.i.d.), in diabetic neuropathy. The frozen databases of these studies were evaluated to determine the findings. Both type 1 and type 2 diabetics were included, comprising 1346 men and women, ages 18-70 years, with at least 1 year of diabetes and no other causes for neuropathy. Exclusionary factors included alcohol or drug abuse, cardiac or liver disease, malignancy or pregnancy. All patients underwent neurological examination, nerve conduction studies, and vibratory detection threshold testing. Efficacy end points included morphometric analysis of sural nerve biopsy at baseline and follow-up, median, peroneal, and sural nerve conduction velocity and amplitude combined in an O'Brien average rank score, as well as index finger and great toe vibratory detection threshold combined in the same fashion. Clinical symptom score was measured by Sima and colleagues on a 0 (no symptoms) to 3 (incapacitating symptoms) scale and a visual analogue score was assessed by the patient. Statistical analysis was undertaken using rank-transformed data in an ANOVA model, O'Brien's average rank scores, and a mixture of linear models to account for heterogeneity in response data.

Although no improvement was demonstrated for any nerve in either conduction velocity or amplitude in patients taking 500 mg or 1000 mg ALC t.i.d., vibratory detection threshold improved significantly and, in biopsied patients, numbers of sural nerve fibers and regenerating clusters increased ($P = 0.049$ and 0.033, respectively). Clinical symptom score demonstrated no signifi-

cant improvement in treated patients compared to placebo. Among 27% of the patients who reported pain as their primary symptom, significant improvement in the visual analog pain score was seen at the 1000 mg-treatment level in 1 study and in the pooled cohorts of both studies at 26 (P = 0.031) and 52 (P = 0.025) weeks. Pain improvement also correlated with significant improvement, in the 1000 mg group, in the O'Brien rank score for biopsy parameters including myelinated fiber regeneration, occupancy, and fiber size. ALC was safe with pain, paresthesiae, and hyperesthesia the most common adverse events. Painful diabetic neuropathy appears to respond to 1000 mg t.i.d. of ALC, but larger, longer trials initiated early in the course of diabetic neuropathy are warranted to confirm these results.

COMMENTARY

Another option for refractory painful neuropathy is methadone, a potent μ agonist and schedule II opioid known best as the staple for the treatment of withdrawal in the drug-addicted. Subsequent to a successful lawsuit brought by the American Pharmaceutical Association in 1976, its analgesic usage has increased, with small clinical trials showing efficacy, more so in patients with peripheral neuropathic, rather than central, pain syndromes. Its use in diabetic neuropathy, despite the absence of adequate clinical trials, is being advocated (Hays L et al. *Diabetes Care.* 2005;28;485-487).

Convincing points may be raised arguing that it is the opioid of choice for persistent neuropathic pain. Apart from its very low cost and ease of administration, unique properties that set it apart from other opioids include its activity as an N-methyl-D-aspartate (NMDA) receptor antagonist, its inhibition of norepinephrine and serotonin reuptake, its trimodal mode of metabolism and excretion encompassing the liver, fecal, and renal routes, precluding the need for dosage adjustment in renal failure, the absence of psychoactive metabolites, and excellent bioavailability due to its lipophilic nature.

If antidepressants or anticonvulsants fail to manage painful diabetic neuropathy, methadone may be an alternative, starting with 0.5-1 mg every 8 h in the elderly, or 2.5-5 mg every 8 h in younger diabetics. Titrate upward weekly with breakthrough doses as needed; the latter will usually encompass not less than 10-20% of the total dose. Side effects, including nausea, vomiting, sweating, pruritus and, rarely, respiratory depression, may warrant lowering the dose by 25% but constipation, the most frequent side effect, requires aggressive attention. Methadone discontinuation, as with any long-acting opioid, should be done slowly. — **MICHAEL RUBIN**

Stroke Center Designation: Will New Administrative Hoops Translate into Improved Care?

ABSTRACT & COMMENTARY

Synopsis: *BAC elements, such as quality of care initiatives and support of the medical organization, did not impact rates of tPA use, but may have had other quality of care effects, such as prevention of stroke-related complications.*

Source: Douglas VC, et al. Do the Brain Attack Coalition's Criteria for Stroke Centers Improve Care for Ischemic Stroke? *Stroke.* 2005;64:422.

THE BRAIN ATTACK COALITION (BAC) PUBLISHED ITS criteria for primary stroke center designation in 2000. Prior literature (primarily from Europe) had shown that stroke units, as opposed to general medical wards, favorably effected discharge disposition and overall mortality. This was primarily a function of preventing complications and implementing rehabilitation services. Somewhat in contrast to this, the primary thrust of the BAC report was on acute stroke care. Its goal was to increase the use of intravenous tissue plasminogen activator (tPA), currently limited to less than 5% of stroke patients in the United States. Campaigns, such as the American Stroke Association's "Get With the Guidelines" program, followed the lead of the BAC. Most recently, the Joint Commission on Accreditation of Healthcare Organizations (JCAHO) began its primary stroke center designation process. With JCAHOs involvement, it is reasonable to assume that every hospital will aspire to achieve its stroke center imprimatur, if for no other reason than to avoid losing a significant portion of patient volume. This includes not only stroke patients, but also patients with other forms of acute central nervous system pathology that may initially mimick or be interpreted as stroke. In the report reviewed here, Douglas and colleagues address the important question of whether these new administrative constructs will

actually increase tPA use and, more importantly, whether they can have measurable effects on stroke morbidity and mortality.

Douglas et al analyzed data from the University HealthSystem Consortium (UHC), with 16,853 patients admitted to the emergency departments of 34 participating hospitals. Seven of the 11 major elements identified by the BAC were correlated with a 2-3 fold increase in tPA administration. These are shown in bold in *Table 1*. In multivariate analysis, 4 of the 7 features remained significantly associated with increased tPA use: written care protocols, emergency medical services (EMS), emergency department (ED), and continuing medical education. The report emphasizes that since speed is the major issue in the delivery of tPA, it is the integration between EMS, the ED, and the stroke team that is the most crucial factor in a hospital's ability to deliver tPA within 3 hours of symptom onset.

The presence of BAC requirements had no impact on in-hospital mortality or likelihood of discharge to home. Douglas et al note that not surprisingly, tPA has been shown to reduce long-term morbidity and not to decrease short term morbidity or mortality. BAC elements, such as quality of care initiatives and support of the medical organization, did not impact rates of tPA use, but may have had other quality of care effects not studied by Douglas et al, such as prevention of stroke-related complications.

Table 1

BAC requirements for stroke center designation

Acute stroke teams
Written care protocols
Emergency medical services
Emergency department
Stroke unit
Neurosurgical services
Commitment of medical organization, stroke center director
Neuroimaging services
Laboratory services
Outcome and quality improvement activities
Continuing medical education

Note: Requirements shown in bold were correlated with a 2-3 fold increase in tPA administration.

Table 2

JCAHO stroke performance measurements

DVT prophylaxis
Discharged on anti-thrombotics
Patients with AF receiving anti-coagulation therapy
TPA considered
Anti-thrombotic medications with 48 hours of hospitalization
Lipid profile during hospitalization
Screen for dysphagia
Stroke education
Smoking cessation
Plan for rehabilitation was considered

COMMENTARY

Recent investigations in our own locale have been done as part of the New York State Department of Health Stroke Center Designation Pilot Project. This study involved 32 hospitals in Brooklyn and Queens (14 of which were designated as stroke centers), and showed improvements in ED door to MD contact time, door to CT scan time, and door to tPA administration. tPA use increased from 2.4% to 7.7% in stroke centers. These data have prompted New York State to initiate a state-wide process of stroke center designation, replicating the methodology of the pilot project.

Stroke certification by JCAHO (*see Table 2*) differs from the NYS program, as it is less stringent and detailed in its requirements for acute stroke treatment (tPA considered), but is much broader overall. JCAHO addresses in-hospital, stroke-related complications (such as prophylaxis for deep vein thrombosis and screening for dysphagia), and also draws attention to secondary stroke prevention (such as discharge on anti-thrombotic medications).

As neurologists, we should embrace the new attention paid to stroke, and campaign for greater stroke-related resources on a hospital, as well as governmental level. We should work to translate these guidelines into palpable clinical benefits for our patients. At the same time, we should work to prevent ourselves from drowning under the deluge of paperwork new regulations will inevitably bring. — **ALAN SEGAL**

CME Questions

13. PEG feeding is preferred to NG feeding in all of the following, except:
a. patients who cannot tolerate an NG tube.
b. patients who frequently extubate themselves.
c. patients who may need long term tube feeding.
d. patients who are terminal.
e. patients who will be permanently institutionalized.

14. Which of the following is TRUE regarding neuromyelitis optica (Devic's syndrome)?
a. It typically affects the cerebral hemispheres.
b. It is diagnosed with oligoclonal antibodies in the CSF.
c. It is associated with a serum antibody against a constituent protein in the blood brain barrier.
d. None of the above

15. Modifiable factors relevant to the prevention of diabetic neuropathy include:
a. total cholesterol, LDL cholesterol, and triglyceride level.
b. body-mass index.
c. hypertension.
d. smoking history.
e. All the above

16. For treatment of painful diabetic neuropathy:
a. methadone is not an option.
b. methadone is the drug of first choice.
c. methadone may rarely cause respiratory depression.
d. methadone starting dose is 10 mg every 4 hours as needed.
e. None of the above

Answers: 13. (d); 14. (c); 15. (e); 16. (c)

Readers are Invited

Readers are invited to submit questions or comments on material seen in or relevant to Neurology Alert. Send your questions to Leslie Hamlin—Reader Questions, Neurology Alert, c/o American Health Consultants, PO Box 740059, Atlanta, GA 30374.

In Future Issues:

Nerve Root Injections

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.*

Preparing for the Possibility of a Bird Flu Pandemic

The possibility of a bird flu pandemic has health officials worldwide in a high state of alert. The highly pathogenic avian influenza A virus is responsible for the death of more than 100 million birds in Southeast Asia, but less than 100 cases have been documented in humans, and only 2 of those have been from human-to-human contact. Still, influenza A viruses are known to undergo an antigenic shift periodically, marking an abrupt change in the viral genome. It is the possibility of a mutation that has health officials concerned. If the virus suddenly became infectious in human populations, the resulting pandemic could kill millions, as similar avian influenza virus pandemics did in 1968, with one to four million deaths, and 1918, when the avian flu pandemic killed as many as 50 million people. The World Heath Organization is urging all countries to develop or update their influenza pandemic preparedness plans. From a pharmaceutical perspective, the WHO has singled out oseltamivir (Tamiflu) as the treatment of choice to reduce symptoms and prevent spread of avian influenza. Roche Holding AG, the makers of oseltamivir, recently announced that Britain and the United States are discussing large purchases of the drug, with the intent of stockpiling supplies for a potential avian influenza outbreak. Other governments around the world have been stockpiling the drug as well, and Roche is increasing its production capacity to meet the additional demand.

Amoxicillin-Clavulanate vs Ciprofloxacin

The search for effective antibiotics to treat common infections is a high priority, given increasing resistance patterns for many commonly used antibiotics. This was the basis for a new study by researchers at the University of Washington, in which they compared ciprofloxacin to amoxicillin-clavulanate in women with uncomplicated cystitis. The study was driven by an increasing rate of resistance to trimethoprim-sulfa and other antimicrobials among *E. coli* strains causing acute cystitis in women. While ciprofloxacin is a common alternative, amoxicillin-clavulanate has not been well studied. In a randomized, single-blinded trial, 370 women aged 18 to 45 with symptoms of acute uncomplicate cystitis with a positive urine culture were randomized to amoxicillin-clavulanate 500/125mg twice daily or ciprofloxacin to 250 mg twice daily for 3 days. Clinical cure was observed in 58% of women treated with amoxicillin-clavulanate, compared with 77% of women treated with ciprofloxacin ($P < .001$). Amoxicillin-clavulanate was not as effective as ciprofloxacin, even among women infected with *E. coli* strains suscepti-

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) 262-5416. E-mail: leslie.hamlin@ thomson.com.

ble to amoxicillin-clavulanate. At follow-up visits 2 weeks after treatment, 45% of women in the amoxicillin-clavulanate group had vaginal colonization with *E. coli*, compared to only 10% in the ciprofloxacin group ($P <$ .001). The authors point out that *E. coli* resistance is an increasing problem worldwide, especially with trimethoprim-sulfa. However, resistance is also been seen with fluoroquinolones including ciprofloxacin. Amoxicillin-clavulanate was chosen in the study in the hopes of finding an effective fluoroquinolone-sparing antibiotic for the treatment of uncomplicated cystitis. Unfortunately, amoxicillin-clavulanate is not a reliable option and alternatives will need to be found (*JAMA.* 2005;293:949-955).

AD Therapy and Cognitive Function

Men with prostate cancer who note worsening cognitive function in the early stages of androgen deprivation (AD) therapy should consider that the change is due to the treatment not the disease, according to new study published online in the "Early View" section of *Cancer*. Researchers from Finland followed 23 men undergoing AD for prostate cancer. Thirty-one cognitive tests were performed at baseline, 6 months, and 12 months into therapy. Testosterone and estradiol locals were followed throughout treatment. Visual memory of figures in recognition speed of numbers were significantly impaired at 6 months. Surprisingly, some men with the lowest change in estradiol levels had an improvement in verbal fluency and 12 months. The author suggests that cognition may be adversely affected during androgen deprivation (*Cancer*-published online 2/16/05).

LDL Lowering in CHD Patients

An LDL target in the 70s for CAD patients may become the standard, as evidence continues to mount for the benefit of intensive cholesterol lowering. The latest study from the "Treating to New Targets" or TNT investigators looked at 10,000 patients with stable coronary disease and LDL levels less than 130. Patients were randomized to atorvastatin 10 mg/day (low dose) or 80mg/day (high dose) and were followed for an average of 4 years. Mean LDL cholesterol was lowered to 101 mg/dL in the low-dose group and to 77 mg/dL in the high-dose group. Persistent elevations in liver enzymes was more common in the high-dose group (0.2% low dose, 1.2 % high dose [$P <$ .001]). The study end points were cardiovascular events including death from CHD, nonfatal MI, resuscitation after cardiac arrest, or stroke (fatal or nonfatal). A primary event occurred in 548 patients in the low-dose group (10.9%) and 434 patients in the high-dose group (8.7%) for a 2.2% absolute rate reduction (HR, 0.78; 95% CI, 0.69-0.89; $P <$ .001). There was a higher death rate from noncardiovascular causes in the high-dose treatment group, and no difference in overall mortality. There were no trends in the noncardiovascular deaths, specifically no higher rate of cancer or violent deaths. The authors conclude that aggressive LDL lowering is warranted in CHD patients (*N Engl J Med*-published online March 2005). An accompanying editorial suggests more caution, stating, "Patients and their physicians will need to carefully weigh the benefits or a reduction in the risk of cardiovascular events. . . against the uncertainty of an increase in the risk of death from noncardiovascular causes" (*N Engl J Med*-published online March 2005).

FDA Actions

The FDA and federal marshals from the Department of Justice have seized Paxil CR and Avandamet tablets manufactured by GlazxoSmithKline at its plants in Knoxville, TN, and Puerto Rico. The FDA stated that the seizures were prompted by violations of manufacturing standards that resulted in the production of poor quality drug products, including tablets that could split apart and tablets that had inaccurate doses of the active ingredient.

In late February, the FDA issued a public health advisory regarding nataluzimab (Tysabri), Biogen's recently approved drug for the treatment of relapsing forms of multiple sclerosis. Marketing of the drug has been suspended while the agency and the manufacturer evaluate 2 cases of progressive multifocal leukoencephalopathy in MS patients who were using the drug, one of which resulted in death. Nataluzimab received accelerated approval in November 2004, and 8000 patients have received the drug, including 3000 who received it during clinical trials. ■