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

Financial Disclosure:

Neurology Alert's physician editor, Fred Plum, MD, is University Professor, Department of Neurology, Cornell University Medical College.

Can Life Span Be Extended in Mammals?

ABSTRACT & COMMENTARY

By M. Flint Beal, MD

Professor and Chairman of the Department of Neurology at Cornell Medical College.

Dr. Beal reports no consultant, stockholder, speaker's bureau, research, or other relationships related to this field of study.

Synopsis: *Overexpression of the antioxidant enzyme catalase, which converts H_2O_2 to H_2O, results in lifespan extension in long-lived mice.*

Source: Schriner SE, et al. Extension of Murine Lifespan by Overexpression of Catalase Targeted to Mitochondria. Sciencexpress/Sciencexpress/www.sciencexpress.org/5 May 2005/Page 1/10.1126/science.1106653

THE ONLY CONSISTENT INTERVENTION, WHICH APPEARS TO EXTEND lifespan in mammals, has been caloric restriction. This has been shown in a number of species, and there are ongoing studies in primates. Patients who voluntarily undergo caloric restriction show improvement in some of the biomarkers which improve in calorically restricted mammals. Other interventions, however, have been largely unsuccessful in extending lifespan.

The oxidative stress theory of aging postulates that age-associated reductions in physiological functions are caused by slow steady accumulation of oxidative damage to macromolecules, which increase with age, and which are associated with reduced life expectancy. This hypothesis was subsequently refined, and it was suggested that mitochondria are the major target of free radical attack associated with aging. Reactive oxygen species are generated in large part from single electrons escaping from the electron transport chain. In strong support of the theory, is new evidence that overexpression of the antioxidant enzyme catalase in mitochondria extends lifespan in mice.

Prior studies had shown that oxidative damage and mitochondrial DNA point mutations accumulate with human aging. We found a 3-fold increase, which correlated with reductions in cytochrome oxidase activity. Other studies in which mitochondrial point mutations are engineered to occur in the mitochondrial genome, reduce lifes-

VOLUME 23 • NUMBER 11 • JULY 2005 • PAGES 81-88

NOW AVAILABLE ONLINE
www.ahcpub.com

pan in mice by 50%. Although some studies in both fruit flies and in mice have suggested that it may be possible to extend lifespan by overexpression of antioxidant enzymes, these studies have been criticized, since they generally have shown efficacy in short-lived strains.

In the study cited above, Shriner and colleagues show that overexpression of the antioxidant enzyme, catalase, which converts H_2O_2 to H_2O, results in lifespan extension in long-lived mice. Shriner et al produced transgenic mice that overexpressed human catalase localized to the peroxisome, the nucleus, and the mitochondria. Only the mice with catalase targeted to the mitochondria showed a significant increase in lifespan. This was approximately a 20% or a 5-month increase in lifespan in 2 founders. There was a similar increase in both median and maximum lifespan. The mice overexpressing catalase showed reduced cardiac pathology, such as sub-endocardial interstitial fibrosis and arteriosclerosis, which occur with normal aging. In addition, there was a reduction in the severity of cataracts at 17 months. The mitochondrial-targeted catalase decreased the mean level of H_2O_2 production from heart mitochondria by 25%, and it prevented the inactivation of aconitase, which is a well-described marker of oxidative damage. It also protected against age-related increases in oxidative damage to DNA in skeletal muscles.

COMMENTARY

These findings are of great interest. They are the first to directly show that overexpression of a free radical scavenging enzyme extends both median and maximum lifespan in mammals. It is of interest that these effects occurred only when the antioxidant enzymes were targeted to mitochondria. The results provide strong evidence that both mitochondrial dysfunction and oxidative damage play a critical role in normal aging and may contribute to pathological processes associated with aging including arteriosclerosis, neoplasia, cataracts, and neurodegenerative diseases. As such, development of safe effective antioxidants may be beneficial in preventing some of these age-related pathologies. ■

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.

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.

THOMSON
AMERICAN HEALTH CONSULTANTS

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 is on the speaker's bureau for Athena Diagnostices and does research for Viatris. Dr. Segal is on the speaker's bureau of Boehringer-Ingelheim. Dr. Plum, Dr. Frucht, Dr. Reich, and Dr. Beal 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.

Autonomic Peripheral Neuropathy

ABSTRACT & COMMENTARY

By Norm Latov, MD

Professor of Neurology and Neuroscience and Director of the Peripheral Neuropathy Center at Weill Medical College at Cornell University.

Dr. Latov is a consultant for Quest Diagnostics and Talecris Inc., is a stockholder of Therapath LLC, and has royalties in Athena Diagnostics.

Synopsis: *The availability of sensitive and reproducible measures of autonomic function has improved physicians' ability to diagnose these disorders.*

Source: Freeman R. Autonomic Peripheral Neuropathy. *Lancet.* 2005;365:1259-1270.

THIS ARTICLE SUMMARIZES OUR CURRENT UNDERstanding of the autonomic neuropathies, their manifestations, causes, mechanisms, and treatments. As these disorders can primarily affect the autonomic nerves, with few other signs of neuropathy, it behooves us to recognize the associated symptoms, so as to consider the diagnosis. Cardiovascular symptoms consist of orthostatic dizziness, headache, or tachycardia. Gastrointestinal manifestations result from gastropareis, with postprandial bloating, nausea or vomiting, or from decreased intestinal motility, with constipation or diarrhea. Genitourinary symptoms can include urinary retention with overflow incontinence, sexual dysfunction resulting from erectile or ejaculatory failure, or reduced vaginal lubrication. Reproducible measures of autonomic function, such as the tilt table test, heart rate variability response, or sudomotor-axon-relex test, are now available, and can be used to confirm the clinical diagnosis and follow progression or response to therapy.

The list of causes for autonomic neuropathy is extensive, and includes diabetes, primary or hereditary amyloidosis, certain genetic defects, autoimmune or paraneoplastic mechanisms, particular infections, including botulism or HIV-1, and some toxins. Freeman and colleagues recom-

mend that testing for causes of autonomic neuropathy be tailored to the individual patient, and depend on the clinical presentation, history, and examination.

Therapy, as in other types of neuropathy, is directed at both the underlying cause and at ameliorating the symptoms. Orthostatic hypotension can respond to volume repletion, with the addition of the mineralocorticoid 9-alpha-fluorohudrocortisone, or of Midodrine, a sympathomimetic agent. Gastroparesis can be treated with frequent small meals and prokinetic agents such as metoclopramide or domperidone. Bowel hypomotility can be improved by increased dietary fiber with fluid, stool softener, and an osmotic laxative. Erectile dysfunction is now commonly treated with phosphodiesterase 5 inhibitors, including sildenafil, tadalafil, or vardenafil, which inhibit breakdown of cAMP and increase smooth muscle relaxation and blood flow. Vaginal lubrication can be helped by the use of vaginal lubricants and oestrogen creams. Intermittent self cathetierization is recommended for therapy of impaired or absent detrusor muscle activity or urinary retention. Most patients can be helped by judicious diagnosis and treatment.

COMMENTARY

The article provides an excellent overview of the autonomic neuropathies, with specific recommendations for diagnosis and treatment. A potential criticism is that the review is not evidence based or based on blinded controlled trials, but relies instead on non-blinded or controlled trials, case series or reports, chapters, review articles, and the author's own experience and expert opinion. However, it represents the best currently available evidence and, as such, is an informative guide to the management of these patients.

Erectile Dysfunction in MS

ABSTRACT & COMMENTARY

By Brian R. Apatoff, MD, PhD

Associate Professor of Neurology at New York Presbyterian Hospital-Cornell Campus.

Dr. Apatoff is on the speaker's bureau of Biogen, Sironea, and Teva.

Synopsis: *It would be reasonable to empirically try sildeanfil and related drugs in both men and women with MS having sexual complaints.*

Source: Fowler CJ, et al. A Double Blind, Randomized Study of Sildenafil Citrate for Erectile Dysfunction in Men with Multiple Sclerosis. *J Neurol Neurosurg Pshchiatry*. 2005;76:700-705.

THIS CONTROLLED, FLEXIBLE DOSE STUDY, WITH an open label extension (OLE), assessed efficacy, quality of life (QoL), and safety in men with MS and erectile dysfunction (ED). Overall, 104 men (mean age, 45; EDSS, 3.97) received sildenfil (25-100 mg) and 113 men (mean age, 47; EDSS, 4.06) received a placebo for 12 weeks. Drug efficacy was assessed by the International Index of Erectile Function (IIEF) questionnaire that includes questions on achieving and maintaining an erection, as well as a global efficacy question. MS patients receiving sildenafil had higher IIEF mean scores ($P < 0.0001$), and 89% (92/103) reported improved erections compared with 24% (27/112) on placebo ($P < 0.0001$). At the end of the OLE phase, 95% of men reported improved erections. Patients receiving placebo during the double blind phase reported a 4-fold improvement in erections once on the drug. Men receiving sildeafil also reported greater improvements in QoL measures. Adverse events were thought to be mild and did not result in discontinuation from the study.

Sexual dysfunction in both men and women with MS can result from a complicated mix of neurological deficits, medication side-effects, and psychological concerns about performance. The incidence of ED in men with MS has been reported to be up to 50-75%, making it a prominent quality of life issue in patient management. ED is commonly associated with the degree of neurogenic urinary dysfunction, so that patients with bladder issues should be queried about ED to offer treatment. Many patients are on SSRIs or other drugs that frequently contribute to loss of libido and sexual dysfunction. Occasionally, patients can have and sustain an erection, but not achieve orgasm and/or ejaculation, possibly in part from relative sensory deficits in these important sacral dermatomes. The use of supraphysiologic stimulation with strong vibrating devices can be helpful in some cases. Since sildenfil was tested in elderly and diabetics with peripheral vascular causes for ED, this controlled trial in MS patients with neurogenic ED is a reassuring validation of this therapeutic approach. Given that MS is predominantly a disorder of women, it would be helpful to see a controlled trial in female patients. Nonetheless, it would be reasonable to empirically try sildeanfil and related drugs in both men and women with MS having sexual complaints.

Brain Inflammation Linked to Autism

ABSTRACT & COMMENTARY

By Barry E. Kosofsky

Attending Pediatrician, New York Presbyterian Hospital, Professor, Cornell Medical College, Research Associate, Massachusetts General Hospital

Dr. Kosofsky reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study.

Synopsis: *This article reports the findings from a neuropathologic study of brain tissue and CSF from autistic patients suggesting an inflammatory-mediated component to this syndrome.*

Source: Vargas DL, et al. Neuroglical Activation and Neuroinflammation in Brain of Patients with Autism. *Ann Neurol*. 2005;57:67-81.

Autism is a disorder which is defined by the DSM-IV as a qualitative impairment in social interaction, a qualitative impairment in communication, and restrictive repetitive and stereotypic patterns of behavior, interests, and activities. Recent studies have suggested an increase in the prevalence of this disorder, thereby, gathering greater public and media attention. Multiple hypotheses including pathological, immunological, environmental, and even iatrogenic contributions to this disorder have been generated.

This neuropathologic report is a case control study displaying an active inflammatory response in CSF samples and post-mortem brain tissue of autistic patients. Brain samples from autistic and control cases were collected from a multi-center Autism Tissue Consortium (including Brain Banks at Harvard, the University of Miami, and the University of Maryland). Autistic cases were defined by DSM-IV criteria and, subsequently, confirmed by the Autism Diagnostic Interview-Revised. Autopsys of brain tissue were conducted on 11 autistic patients and 6 controls. Regions selected for study included the middle frontal gyrus, anterior cingulate gyrus, and cerebellar hemisphere. CSF samples from autistic and control patients were obtained from the Johns Hopkins Neurology CSF repository. The pathology studies used included immunocytochemical staining and confocal microscopy-based quantitative analyses of immunoreactivity for GFAP and HLA-DR, protein tissue arrays, and ELISA studies.

The study shows an increase in innate immune reactivity rather than adaptive immunity in triggering neuroglial activation, a process which was significantly more evident in the brains and CSF of autistics vs controls. Neuropathological studies revealed increased microglial and astroglial activation in all brain areas studied, which was most evident in the cerebellum. Specifically, in the autistic brains, patchy neuronal loss was observed most prominently in the Purkinje cell layers and the granular cell layers of the cerebellum. These were not found in the control samples. In comparison to controls, GFAP immunostaining of the autistic brains revealed increased astroglial activation and reactivity in all regions studied. Immunocytochemical staining for MHC class II markers revealed increased microglial activation more prominently in the cerebellum, as well as the cortex of autistics vs controls. Age, history of developmental regression, or mental retardation in the autistics did not appear to make a significant difference in the amount of microglial or astroglial activation. However, history of epilepsy accounted for elevated microglial activation, which was restricted to the cerebellar white matter of autistic patients.

Other major pathologic findings were the lack of adaptive immunity in the autistic patients. In particular, there was lack of specific T-cell responses and antibody-mediated reactions. However, there was a significant finding of membrane attack via complement, which formed complexes in the purkinje cell and and granular cell layer of the cerebellum. This suggests a possible mechanism of brain damage via microglial activation, triggering complement activation, leading to neuronal loss in the cerebellum.

Brain and CSF studies of autistic patients revealed differences in cytokine expression. In the autistic brains, MCP-1 and TARC (pro-inflammatory chemokines) and TGF-B1 (an anti-inflammatory cytokine) were increased. MCP-1 was found to be significantly increased in both brain and CSF samples. CSF studies from 6 living autistics and 6 controls (without documented CNS pathology) revealed a 12-fold increase in MCP-1 levels. Other proinflammatory and modulatory cytokines and growth factors were also significantly increased.

COMMENTARY

Vargas and colleagues suggest that these findings may reflect disease chronicity, but their findings do not preclude the possibility that these immune mechanisms are invoked in earlier stages of autism. Whether inflammatory changes in the

brains of autistics are the cause or the consequence of this disorder remains to be determined. Likewise, it will be important to establish whether such immune mechanisms contribute to disease progression in a subset of patients with this syndrome. If such a subset could be identified with genetic and/or CSF markers, that would have both diagnostic and therapeutic implications. ■

Pregabalin for Diabetic Neuropathy

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology at Weill Cornell Medical College and Attending Neurologist at New York Presbyterian Hospital.

Dr. Rubin does research for ASTA Medica and Eli Lilly.

Synopsis: *Pregabalin appears to be a safe and effective alternative in the treatment of painful diabetic neuropathy.*

Source: Richter RW, et al. Relief of Painful Diabetic Peripheral Neuropathy with Pregabalin: A Randomized, Placebo-Controlled Trial. *J Pain*. 2005;6:253-260.

In this latest quest for the panacea of painful diabetic neuropathy, diabetics with 1-5 years of painful neuropathy were recruited over a 1-year period to determine the efficacy and safety of 6 weeks of pregabalin, 150 mg or 600 mg/d orally, compared to placebo. Diagnosis of neuropathy was confirmed by history and physical examination. Inclusion criteria included hemoglobin A1c level < 11%, ongoing moderate-to-severe neuropathic pain, as measured by a visual analog scale score > 39 on the Short Form-McGill Pain Questionnaire, and a daily average score > 3 for 4 or more days during a 1-week baseline. Pregnant patients and those with other causes of peripheral neuropathy, serious medical disorders, other neurologic conditions, or recent enrollment in investigational drug trials were excluded. Concomitant pain medications, including tricyclic antidepressants, antiepileptic medication, opioids, capsaicin, and mexiletine were discontinued up to 30 days prior to study drug administration. Aspirin, acetaminophen, and serotonin reuptake inhibitors were permitted without change of dosage. Patients were randomized and, over 2 weeks, titrated upward from 25 mg/d to 150 mg/d (n = 79) or from 100 mg/d to 600 mg/d (n = 82), which they maintained for 4 weeks. Daily pain measurements were the primary end points, while secondary end points included pain characteristics, sleep interference, health status as measured by the 36-Item Short-form Health survey, psychologic state as measured by the Profile of Mood States, and global improvement as measured by the Clinician and Patient Global Impression of Change.

Compared to placebo, pregabalin 600 mg/d significantly lowered mean pain scores, visual analog scale scores, present pain intensity, and effective and total scores on the Short Form-McGill Pain Questionnaire. Sleep interference was significantly lowered and was associated with better Clinician and Patient Global Impression of Change evaluations. Pregabalin 150 mg/d was no more efficacious than placebo. Dizziness (37.8%), somnolence (22%), peripheral edema (17.1%), headache (15.9%), and asthenia (12.2%) were the most common adverse effects in the 600 mg/d group, but was usually graded no worse than mild-to-moderate in severity. Pregabalin appears to be a safe and effective alternative in the treatment of painful diabetic neuropathy.

COMMENTARY

Which oral medication is best for diabetic neuropathic pain with respect to safety and tolerability, the latter as assessed by the incidence of drug-related adverse events and study discontinuation resulting thereof? Review of English-language, placebo-controlled and direct-comparison studies of drug trials for painful diabetic neuropathy, published from 1990 to November 2203, was undertaken to answer this question (*Diab Metab Res Rev*. 2005;21;231-240). MEDLINE, EMBASE, and the Cochrane Controlled Trials registry library 2003 were utilized, and key search words included diabetic peripheral neuropathy and drug therapy. Topical treatments were excluded, as were studies involving other painful conditions such as post-herpetic neuralgia and cancer, and only randomized controlled trials were included.

Nineteen placebo-controlled and 5 comparative trials met the search criteria. Treatment duration ranged from 2-52 weeks, and enrollment ranged from 14-333 patients. End points varied and included pain scales (Likert, Gracely, visual analog) or questionnaires (Short Form-McGill Pain).

Tricyclic antidepressants were plagued by dose-limiting side effects, both annoying (dry mouth, constipation, sedation, weight gain) and potentially serious (urinary retention, orthostatic hypotension,

cardiac conduction defects). Selective serotonin reuptake inhibitors (SSRIs) demonstrated only weak benefit. Tramadol and oxycodone similarly demonstrated side-effect limitations. Carbamazepine, lamotrigine, and sodium valproate are alternatives that would benefit from further study. Dilantin has no role in the treatment of diabetic neuropathy and may exacerbate glucose control due to its inhibitory effect on insulin secretion. Gabapentin was effective and well tolerated with little drug interaction and appears to be the preferred agent, particularly in the elderly. However, not surprisingly, more studies are needed. ■

Vitamin E, Donepezil and MCI

ABSTRACT & COMMENTARY

By Norman R. Relkin, MD, PhD

Associate Professor of Clinical Neurology and Neuroscience at New York Presbyterian Hospital-Cornell Campus.

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

Synopsis: *The rate of development of dementia in patients with MCI can be altered by a medical intervention, in this case by administration of an acetylcholinesterase inhibitor.*

Source: Petersen RC, et al. Vitamin E and Donepezil for the Treatment of Mild Cognitive Impairment. *N Engl J Med*. 2005;352(23):2379-2388.

Mild cognitive impairment (MCI)is a recognized prodrome to dementia and amnestic forms of MCI progress most commonly to Alzheimer's disease (AD). The Alzheimer's Disease Cooperative Study (ADCS) Group investigated the effects of alpha-tocopheral (Vit E) and donepezil (Aricept ®) on progression of amnestic MCI to AD. In a 3-year multicenter study involving 769 MCI patients, they randomly assigned subjects to receive either placebo, 2000 IU Vit E or 10 mg donepezil daily in a double-blind treatment protocol. Approximately 28% of subjects progressed to frank Alzheimer's during the course of the trial, representing an annual conversion rate of 16%. Vitamin E had no impact on the rate of conversion, whereas donepezil significantly reduced the likelihood of progression to AD in the first 12 months. Donepezil did not alter the 3-year conversion rate except among persons carrying the APOE-e4 allele, for whom the benefits were maintained over the full 3 years of the trial. APOE carrier status had no impact on results with vitamin E. The occurrence of adverse events with donepezil and vitamin E was generally comparable to that previously reported with these agents in Alzheimer patients, as was mortality during the period of treatment. This study is among the first to suggest that rate of development of dementia in patients with MCI can be altered by a medical intervention, in this case by administration of an acetylcholinesterase inhibitor.

COMMENTARY

There are several noteworthy findings in this ADCS study. The observed 16% annual conversion rate from MCI to AD validates predictions for patients meeting Petersen's criteria for amnestic MCI. This illustrates that it is possible to identify persons with a relatively high likelihood of developing Alzheimer's in the next 3-5 years by careful patient selection. While this may make amnestic MCI a good construct for future AD prevention trials, patients meeting these criteria represent only a very small percentage of the total population, and it is likely to be challenging for physicians to identify such individuals in routine clinical practice.

Vitamin has been used in the treatment of AD since a previous ADCS study suggested that high doses (2000 I.U./day) could forestall the development of major impairments in patients with symptomatic AD. This reported benefit of Vitamin E has not been subsequently confirmed, and the failure of Vitamin E to slow progression of MCI to AD is a blow to those who advocate anti-oxidant treatment for AD. A recent meta-analysis found that vitamin E doses in excess of 400 IU per day were associated with increased morbidity, bringing into question the wisdom of administering 5x higher doses to elderly AD patients.

The effects of donepezil on progression of AD in the study cohort as a whole reached statistical significance in the first year only, which is comparable to the period of time in which AD patients responding to this agent experience improvement of their cognitive decline above baseline. It is, therefore, not possible to say on the basis of this trial whether donepezil exerts a true protective effect against AD or simply delays a formal AD diagnosis by virtue of symptomatic benefits that maintain cognitive status above the cutoff for dementia. The possibility that donepezil and other acetylcholinesterase inhibitors exert neuroprotective effects is currently under study in light of recent findings that rate of hippocampal and cortical atrophy may be slowed by these agents.

The results were more dramatic among MCI patients with the APOE-4 allele, who were a third less likely to develop AD over 3 years with donepezil treatment than those receiving placebo. The rate of progression to AD was considerably higher among 4 carriers, with 76% of those who converted to AD during the trial possessing at least one APOE-4 allele. While the possibility of an interaction between APOE and cholinesterase treatment cannot be ruled out, the more likely explanation for the observed risk reduction is that MCI patients who are APOE-4 carriers are more likely to progress to AD in the time span of the trial, providing a better signal for observing the benefits of cholinesterase inhibition.

Since the primary outcome measure of this trial was negative, further studies will be needed before evidenced-based treatment of MCI can be carried out. However, this trial demonstrates that progression from mild impairment to frank dementia need not be considered inexorable, and its rate may be altered by available treatments. ■

Spinal Epidural Abscess

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Synopsis: *Patients with spinal epidural abscess may be normothermic and have normal WBC counts. Urgent surgery was more likely to be offered to patients presenting with neurologic deficits than with pain alone. Patients treated without early surgery were significantly more likely to deteriorate and suffer poor outcomes.*

Source: Curry WT et al. Spinal Epidural Abscess: Clinical Presentation, Management, and Outcome. *Surg Neurol*. 2005;63;364-371.

SPINAL EPIDURAL ABSCESS IS A RARE HOSPITAL admission, perhaps 1 in 10,000, and mortality remains high, up to 31%. Records of patients admitted to the Massachusetts General Hospital with this diagnosis between 1995 and 2001 were retrospectively reviewed to determine its clinical characteristics and assess whether outcome could be foretold based on presentation and treatment. Only those with pathologic or radiographic evidence of spinal epidural abscess were included, whereas those with discitis or osteomyelitis alone were excluded. Patients were grouped based on antibiotic or surgical treatment and worsening status was based on physician's notes in the chart. Statistical analysis included Student t test and Pearson chi square test.

Fourty-eight patients, 30 men and 18 women, mean age 61 years (range, 31-84 years), were seen during the study period. Intravenous drug abuse was identified most often (27%, n = 13) as a risk factor. Nonspinal infection (21%, n = 10), diabetes, alcoholism, spinal procedures or trauma, HIV, and chronic steroid use were associated in the remainder. Weakness or sphincteric dysfunction (57%, n = 27), fever > 101 (48%, n = 23), and radicular or axial pain (35%, n = 17) were the most common presenting features. Normal peripheral white blood count did not exclude the diagnosis, and erythrocyte sedimentation rates (ESR) were rarely obtained. Blood cultures were positive in 60% (n = 30), with *S. aureus* the most commonly identified organism (63%, n = 29). Heterogeneously enhancing epidural collections were the typical MRI finding, iso/hypointense on T1 and hyperintense on T2 weighted images, most often in the lumbosacral (46%, n = 22) or cervical region (23%, n = 11), spanning anywhere from 1 to 13 levels. Osteomyelitis or discitis was evident in 73% in the adjacent disc or vertebral body. Fifty-two percent (n = 25) underwent urgent surgery, generally those with neurologic deficits, and 48% (n = 23) initially received antibiotics alone, usually those with only pain or fever. Of the latter, 23% (n = 11) required delayed surgery. On discharge, 37.5% (n = 18) were neurologically improved, 33% (n = 16) were unchanged, and 29% (n = 14) had worsened, compared to status on admission. Of those improved, 83% (n = 15) had undergone surgery, whereas among those who deteriorated, 86% (n = 12) had received antibiotics initially. Of the unchanged patients, 50% each (n = 8) had received antibiotics or undergone surgery. Fever and elevated white count may be absent in patients with spinal epidural abscess, and those who receive early surgery are likely to do better than those initially treated with antibiotics alone.

■ COMMENTARY

A recent series confirms the notion that surgically treated patients with spinal epidural abscess do well (*Surg Neurol*. 2005;63;S1:26-S1:29). Among 24 patients, 17 men and 7 women, mean age was 47.5 years (range, 17-73 years), with spinal epidural abscess between January 1986 and December 2003; 21 (87.5%) underwent surgical drainage of the abscess. Sixty-two percent were immuno-compromised as a result of concomitant illness, including diabetes or infection, with intravenous drug abuse, spinal

trauma, cancer, and gunshot wound as other predisposing factors. Presenting complaints included back pain (100%), muscle weakness (66.6%), paresthesiae (38%), or sphincteric dysfunction (33.3%). Causative organisms included *S. aureus* (n = 14, 58.3%), tuberculosis (n = 3, 12.5%), *E. coli*, and *S. epidermidis* (1 each, 4.2%). Normal function was regained in 62.5% (n = 15), with 4 remaining with neurologic disability. Early surgery combined with antibiotic therapy appears to be the treatment of choice for spinal epidural abscess. ■

CME Questions

1. **The best oral agent for the treatment of diabetic neuropathy in the elderly is probably:**
   a. gabapentin
   b. carbamazepine
   c. lamotrigine
   d. sodium valproate
   e. None of the above

2. **Presenting symptoms or signs of spinal epidural abscess always include:**
   a. elevated sedimentation rate
   b. elevated temperature
   c3. elevated white blood cell count
   d. back pain
   e. None of the above

Answers: 1. (a); 2. (e)

Correction

Beginning with the April issue of *Neurology Alert*, we began to print the Volume # as 24 when it should have read Volume 23. The error continued from the April issue through to the June issue. Please note the correction. ■

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, Clinical Cardiology Alert, c/o American Health Consultants, PO Box 740059, Atlanta, GA 30374. ■

In Future Issues:

Imaging Depression in Parkinson's Disease: Role of the Limbic System

Thomson American Health Consultants
Building Six, Suite 400
3525 Piedmont Road NE
Atlanta, Georgia 30305-1515
Tel (404) 262-7436 Fax (404) 262-7837
www.ahcpub.com

THOMSON
AMERICAN HEALTH CONSULTANTS

Dear Neurology Alert Subscriber:

This issue of your newsletter marks the start of a new Continuing Medical Education (CME) semester and provides us with an opportunity to review the procedures.

Neurology Alert provides you with evidence-based information and best practices that help you make informed decisions concerning treatment options and physician office practices. Our intent is the same as yours - the best possible patient care.

The objectives of Neurology Alert are to:

- present current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;
- discuss the pathogenesis and treatment of pain;
- present "basic science" lessons in brain function;
- discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs; and
- discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness.

Each issue of your newsletter contains questions relating to the information provided in that issue. After reading the issue, answer the questions at the end of the issue to the best of your ability. You can then compare your answers against the correct answers provided in an answer key in the newsletter. If any of your answers were incorrect, please refer back to the source material to clarify any misunderstanding.

At the end of each semester you will receive an evaluation form to complete and return in an envelope we will provide. Please make sure you sign the attestation verifying that you have completed the activity as designed. Once we have received your completed evaluation form we will mail you a CME certificate.

If you have any questions about the process, please call us at (800) 688-2421, or outside the U.S. at (404) 262-5476. You can also fax us at (800) 284-3291, or outside the U.S. at (404) 262-5560. You can also email us at: ahc.customerservice@thomson.com.

On behalf of Thomson American Health Consultants, we thank you for your trust and look forward to a continuing education partnership.

Sincerely,

Brenda Mooney
Vice-President/Group Publisher
Thomson American Health Consultants