Providing Evidence-based Clinical Information for 24 Years

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

AHC Media LLC Home Page—www.ahcmedia.com

CME for Physicians—www.cmeweb.com

AHC Media LLC

INSIDE

Financial Disclosure:

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

SPORTing Statistics: Slicing the Drive on Appropriate Treatment for Herniated Lumbar Discs

ABSTRACT & COMMENTARY

By Justin F. Fraser, MD, Roger Hartl, MD, and John Boockvar, MD

Department of Neurological Surgery Weill Medical College of Cornell University, New York, NY

Dr. Fraser, Dr. Hartl, and Dr. Boockvar report no financial relationship relevant to this field of study.

Synopsis: *Both conservative and surgical therapies are effective in the treatment of herniated lumbar discs.*

Sources: Weinstein JN, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT) observational cohort. *JAMA.* 2006;296(20):2451-2459 and Weinstein JN, et al. Surgical vs nonoperative treatment for lumbar disk herniation: the Spine Patient Outcomes Research Trial (SPORT): a randomized trial. *JAMA.* 2006;296(20):2441-2450.

HERNIATED LUMBAR DISCS ARE A DEBILITATING NEUROLOGICAL problem for many patients. While surgical microdiscectomy is a vital treatment of this disorder, 'conservative' management includes patient education, physical therapy, acupuncture, local steroid injections, oral anti-inflammatory and pain medication, and external orthotics. Given variations in treatment paradigms, Weinstein and colleagues undertook the Spine Patient Outcomes Research Trial (SPORT) to compare conservative treatment vs microdiscectomy for patients with herniated lumbar discs and persistent symptoms, despite conservative treatment for at least 6 weeks. In recognition of the problems of randomization for elective surgery and patient preference/crossover, SPORT was designed as a dual-arm study with a randomized branch and a prospective, cohort branch. Of 1991 eligible patients, 501 were randomized, 743 enrolled in the observational cohort, and 747 refused to participate. While intent-to-treat analysis demonstrated improvement in both surgical and conservative treatment groups with a trend toward greater improvement in the surgical group, there was no statistically significant difference between

VOLUME 25 • NUMBER 6 • FEBRUARY 2007 • PAGES 41-48

NOW AVAILABLE ONLINE
www.ahcmedia.com

groups. However, given the frequent crossover, the study group also performed an as-treated analysis that demonstrated a strong and significant benefit in the surgical group at all follow-up intervals. Additionally, the observational cohort study demonstrated a greater improvement in the surgical group compared to the conservative group.

COMMENTARY

Weinstein, et al, are to be congratulated for their work in attempting to answer a difficult question in treatment of spine disease. In conducting both intent-to-treat and as-treated analysis, and in publishing results from both prospective-randomized and observational-cohort arms, they make a valiant effort to provide the most appropriate statistical comparison of surgical and nonsurgical treatment. The essential question for any trial of this magnitude is: How will it affect practice patterns for spine surgeons and for physicians who refer patients for non-surgical and surgical therapy? The answer is that it should not; it reaffirms common practice for management of one-level lumbar disc herniations, and its limitations prevent it from providing level-one evidence in comparing surgical to non-surgical management.

Currently, patients referred to our institution for symptomatic nerve-root compression from a lumbar disc herniation are recommended for nonsurgical management prior to consideration for surgery. Operative indications typically include worsening symptoms despite conservative management, progressive neurologic deficit, or severe disability limiting quality of life. While SPORT reaffirms this practice, it also demonstrated that patients presenting with the above conditions are more likely to elect surgery.

Although demonstrating the success of a 'conservative-first' approach, SPORT falls far short of successfully declaring surgical and nonsurgical management to be at equipoise. The limitations of the study are particularly important because of the inappropriate interpretation of the results by the lay media. Despite the as-treated analysis and cohort data showing the superiority of surgical treatment, the intent-to-treat results, that showed no difference, garnered unjustified media exposure. According to ABC News, "Patients suffering from lower back pain could get the same benefits in pain relief and function from nonsurgical treatment as from back surgery...".[1] Medical News Today reported that, "[i]f you suffer from a ruptured disk in your lower back you will recover whether you have surgery or not."[2] While such reports hold little academic interest to spine surgeons, they are important informational resources to our patients. With such sound bytes, patients may question whether surgery carries any benefit. Furthermore, internists and neurologists may hesitate to refer patients based upon such a superficial reading of the study results. As academic medical practitioners, we have a responsibility to understand study limitations, to dispel inappropriate interpretations, and to inform patients on how SPORT impacts our practice.

The most prominent limitation was the extremely high crossover rate: 40% of patients randomized to surgery did not undergo an operation, while 45% of patients randomized to nonsurgical management underwent an operation. While the as-treated analysis showed a clear benefit of surgery, the fact that no statistically significant difference was found in the intent-to-treat analysis may reflect the fact that both groups (as analyzed under intent-to-treat) had significant numbers of both surgically and non-surgically managed patients. With the intent-to-treat analysis essentially meaningless, the as-treated analysis and cohort study results show a clear benefit of surgical intervention. However, as noted in an editorial accompanying the study, Dr. David Flum recognized the important limitation of placebo effect in elective surgical procedures.[3] In any study in which patients elect for a surgical intervention over nonsurgical management, there is an expectation of benefit. That expectation may cloud subjective patient-reported results, rendering the placebo effect an important variable. This is recognized by the lay media. *Newsweek* reports, "[i]n general, researchers put less stock in observational studies than in randomized ones, in part because of the possibility of a placebo effect."[4] However, this problem affects non-blinded randomized studies as well. The question is: Did the placebo effect have equal impact upon

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media LLC, 3525 Piedmont Road., NE, Building. 6, Suite 400, Atlanta, GA 30305.

SENIOR VICE PRESIDENT/
GROUP PUBLISHER: Brenda Mooney.
ASSOCIATE PUBLISHER: Lee Landenberger.
ASSOCIATE MANAGING EDITOR: Jennifer Corbett.
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@ahcmedia.com
Editorial E-Mail Address: jennifer.corbett@ahcmedia.com
World-Wide Web: www.ahcmedia.com

Subscription Prices
United States
1 year *with* free AMA Category 1 credits: $289
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

AHC Media LLC is accredited by the Accreditation Council for Continuing Medical Education to provide continuing medical education for physicians.

AHC Media LLC designates this educational activity for a maximum of *25 AMA PRA Category 1 Credits™*. Physicians should only claim credit commensurate with the extent of their participation in the activity.

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 **Jennifer Corbett**, Associate Managing Editor, at (404) 262-5431.

patients in the randomized and observational arm? This question is not answered by SPORT in its current publication. It would be interesting to see the separate analysis of patients who remained within their randomized group, excluding patients who crossed over. Thus, it would be academically negligent to affirm the intent-to-treat analysis without strongly conceding the crossover limitation, and without acknowledging the as-treated and observational cohort results. Therefore, we view the Sport Patient Outcomes Research Trial as a successful affirmation of our conservative-first approach to lumbar disc herniation, but also view the results as supporting the benefits of surgical decompression. ■

References

1. Karalakulasingam C. Beating Lower Back Pain — Without Surgery [online]. Available at: http://abcnews.go.com/Health/story?id=2670812&page=1.
2. Nordqvist C. Patients With Back Pain Recover Without Surgery [online]. Available at: http://www.medicalnewstoday.com/healthnews.php?newsid=57328.
3. Flum DR. Interpreting surgical trials with subjective outcomes: avoiding UnSPORTsmanlike conduct. *JAMA*. 2006;296(20):2483-2485.
4. Springen K. To Cut Or Not To Cut. In: *Newsweek*. 2006; 148(23):58.

FDDNP PET in Mild Cognitive Impairment

ABSTRACT & COMMENTARY

By Brian Apatoff, MD, PhD

Director, Multiple Sclerosis Clinical Care and Research Center, Department of Neurology and Neuroscience, NewYork-Presbyterian Hospital, Cornell Campus

Dr. Apatoff is on the speaker's bureau for Biogen and Teva.

Synopsis: *PET imaging using the novel radioligand FDDNP shows promise in the early diagnosis of Alzheimer's disease.*

Source: Small Gary W, et al. PET of Brain Amyloid and Tau in Mild Cognitive Impairment. *N Engl J Med.* 355;2652-2663.

PET IMAGING WITH FDDNP HAS BEEN PREVIOUSLY used to visualize amyloid plaque and neurofibrillary tangle pathology in the brains of living patients with Alzheimer's disease (AD). A recent study examined whether FDDNP could be used to distinguish normals and AD patients from persons with Mild Cognitive Impairment (MCI), who are at increased risk for developing AD. Gary Small and colleagues at UCLA used 18F-FDDNP as well as other imaging methods to scan 108 volunteers with self-reported memory problems, including 25 with Alzheimer's, 28 with MCI and 30 who were cognitively normal. Usable data was obtained in 83 cases. A subset of 12 subjects (9 normals and 3 MCI) were re-scanned after a period of 17-34 months.

The global levels of FDDNP uptake in the brain were highest in the AD patients, intermediate in MCI, and lowest in normals. The same pattern was observed when the analysis was focused on either the temporal, parietal or posterior cingulate regions. Two out of 3 individuals with MCI who were re-scanned after several months showed increased global FDDNP uptake compared to baseline. Five normal subjects had higher FDDNP uptake on their follow-up studies. Although none of the normals qualified for a diagnosis of MCI on follow-up, one with increased FDDNP uptake on the second scan showed worsening on memory test performance. One subject with AD who died during the study period underwent brain autopsy and was documented to have a significant numbers of plaques and tangles in regions that had shown high FDDNP uptake during life.

Although the mean values of FDDNP uptake differed between AD, MCI and normal groups in a statistically significant way, the individual values overlapped considerably across groups. Nevertheless, the authors concluded that FDDNP can be used to distinguish persons with MCI from normals and AD patients.

■ COMMENTARY

FDDNP is a small lipophilic molecule that crosses the blood-brain barrier and binds to plaque and tangle pathology sufficiently to be visualized on PET scans. Very few centers outside of UCLA, where the radioligand was developed, have tested this approach to antemortem imaging of Alzheimer neuropathology. This study provides further evidence of the validity of FDDNP imaging to the extent that the PET findings correlated well with diagnoses by expert clinicians. The study also indicates that the technique is sensitive; pathology was detected in patients with very mild degrees of impairment. The study does not speak to clinical utility of FDDNP PET for a number of reasons. First, nearly 1/5 of those scanned were disqualified from the analyses, either due to non-AD diagnoses or movement artifacts. The test performed well in distinguishing AD from normal, but there was considerable overlap between these groups and MCI. In the present study, FDDNP has been shown to differentiate a group of AD patients from a group with MCI, but its application

to diagnosis in individuals or in predicting which normals or MCI patients will develop AD remains uncertain. There is little information available about the specificity of the technique, which is an important issue from the standpoint of clinical applicability. Further studies will be needed to evaluate whether this technology, one of several promising PET techniques now under development, can contribute to clinical differential diagnosis of dementia in general and early diagnosis of AD in particular. ■

Is the Sleepy Parkinson's Patient Able to Drive Safely?

ABSTRACT & COMMENTARY

By Charles P. Pollak, MD

Professor, Clinical Neurology, Weill College of Medicine

Dr. Pollak is a stockholder for Merck, and is on the speaker's bureau for Merck.

Synopsis: *Parkinson's patients with daytime sleepiness should drive with a companion.*

Source: Amick MM, et al. Excessive daytime sleepiness and on-road driving performance in patients with Parkinson's disease. *J Neurol Sci*. 2007;252:13-15.

PATIENTS WITH PARKINSON'S DISEASE (PD) ARE vulnerable to a variety of sleep disorders and often have excessive daytime sleepiness (EDS), especially if they are treated with dopamine agonists (DAs) such as pramipexole or ropinirole. It has been suggested that "attacks" of sleepiness may occur without warning in such patients, putting themselves and others at risk. The present investigation was undertaken to assess the ability of patients with PD to drive safely, using a standardized on-road evaluation.

Twenty-one men and women with PD who were not demented and had valid drivers' licenses were administered a standardized road test by a professional driving instructor. Of the 21subjects, 14 received a "safe" driving evaluation, whereas 7 were considered "marginal." Ratings were not explained by differences in EDS (which affected 5 subjects). Thirteen subjects were treated with a dopamine agonist (DA — pramipexole, ropinirole or pergolide). Those so treated had higher self-ratings of sleepiness (Epson sleepiness scale), but their road-test scores were not affected.

■ COMMENTARY

This small, preliminary study confirms that sleepiness is indeed common in patients with PD, especially those treated with DAs. Although 7 of the 21 PD patients were rated as "marginal" rather than "safe" drivers, neither EDS nor use of DAs accounted for their driving performance. It is a pity that a larger sample was not studied, as it might well have demonstrated an adverse effect of EDS on driving performance; even a small effect may prove fatal on the highway. The authors correctly suggest that the presence of a driving instructor may have kept the PD subjects alert. Longer drives (the duration of the road test that was administered was not specified) or tests of motor performance done with a driving simulator might have revealed alarming effects of EDS or of DAs that the present results only hint at. The authors themselves felt obliged to recommend that PD patients with EDS drive with companions, presumably to prod them awake whenever necessary. ■

Neurological Manifestations in Sjögren Syndrome

ABSTRACT & COMMENTARY

By John J. Caronna, MD

Vice-Chairman, Department of Neurology, Cornell University Medical Center, Professor of Clinical Neurology, NewYork-Presbyterian Hospital

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

Synopsis: *Approximately one half of patients who meet current criteria for the diagnosis of primary Sjögren syndrome have clinical or laboratory evidence for peripheral neuropathy.*

Source: Gøransson, LG, et al. Peripheral Neuropathy in Primary Sjögren Syndrome. A Population-Based Study. *Arch Neurol*. 2006;63:1612-1615.

PRIMARY SJÖGREN SYNDROME (PSS), AN AUTO-IMMUNE disease that affects the exocrine glands, is characterized clinically by keratoconjunctivitis sicca and xerostomia. The histologic hallmark of PSS is focal infiltration of the salivary glands by mononuclear lymphoid cells. More than half of patients develop extraglandular manifestations such as myalgias, arthralgias, and pulmonary and gastrointestinal involvement. Gøransson and associates investigated the prevalence and pattern of peripheral nerve involvement in PSS patients selected using new, more stringent criteria.[1]

The authors reviewed the medical records of all patients diagnosed with PSS between 1980 and 2004 at a university hospital in Norway. Of 67 patients who fulfilled the revised international classification criteria for PSS, 62 (8 men and 54 women) agreed to participate in the study (Table 1). Their mean + SD duration of disease was 12 + 10 years (range 0-48 years). Twenty-eight of 62 were not receiving medication for PSS. Among

Table 1. Symptoms and Signs in 62 PSS Patients		
Symptoms or Signs	No. (%) of patients	(after Gøransson, et al)
Ocular symptoms	52	(84)
Ocular signs	46	(74)
Oral symptoms	56	(90)
Salivary gland involvement	46	(74)
Anti-SS-A or anti-SS-B antibodies	52	(84)

those receiving medication for PSS, 24 were taking antimalarial drugs, 14 were taking corticosteroids, and 6 were taking immunosuppressant drugs.

Seventeen patients (27%) had signs of peripheral neuropathy (PN) on clinical examination. The results of nerve conduction studies (NCS) were abnormal in 34 patients (55%): 19 patients (31%) had motor neuropathy, 8 (13%) had sensory neuropathy, and 7 (11%) had sensorimotor neuropathy. In 15 patients the only abnormal finding was an increased F-wave latency in 2 or more nerves. Ten patients had unilateral (n = 8) or bilateral (n = 2) carpal tunnel syndrome, and 3 had abnormal NCS due to local nerve injuries unrelated to PSS.

No significant differences were found on skin biopsy in the density of intraepidermal nerve fibers (IENF) between the calf and the thigh. Mean IENF densities in the leg were significantly lower in PSS patients compared with normative values[2] and values in patients with systemic lupus erythematosus.[3] Two PSS patients had IENF densities less than 3.4 fibers/mm., thereby meeting the morphologic criteria for small-diameter nerve fiber neuropathy. NCS results were normal in these 2 patients. No associations between abnormal clinical findings and IENF densities in the leg or thigh were detected.

COMMENTARY

The authors investigated peripheral nervous system involvement in patients with PSS. They applied the new classification criteria1 to ensure that only patients with true autoimmune PSS were included and patients with SICCA syndromes due to other causes were excluded. Using clinical, electrophysiologic, and morphometric examinations, they identified PN in about one-half of the PSS patients studied (34/62). In half of these (17/34), the PN was subclinical.

Several mechanisms could underlie the demyelinating neuropathy in PSS. Previous authors have reported vascular and perivascular inflammatory infiltrates involving the vasa nervorum in peripheral nerve biopsy specimens.[4,5] The present study has given new impetus to the search for antibodies with reactivity against the proximal regions of sensory and motor nerves and neurons.

References

1. Vitali C. et al. *Ann Rheum Dis.* 2002;61:554-558.
2. Gøransson LG, et al. *Neurology.* 2004;62:774-777.
3 Gøransson LG, t al. *Arch Neurol*. 2006;63:1410-1413.
4 Mellgen, SI, et al. *Neurology.* 1989;39:390-394.
5. Griffin, JW, et al. *Ann Neurol*. 1990;27:304-315.

Pain Prevalence in Multiple Sclerosis

ABSTRACT & COMMENTARY

By Gregg L. Caporaso, MD, PhD

Assistant Professor of Neurology and Neuroscience, Weill Cornell Medical College.

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

Synopsis: *Pain is a common symptom in patients with multiple sclerosis that significantly impairs quality of life yet is often inadequately treated.*

Source: Hadjimichael O, et al. Persistent pain and uncomfortable sensations in persons with multiple sclerosis. *Pain.* 2007;127:35-41.

Pain is among the most common symptoms in patients with multiple sclerosis (MS), but reports on the prevalence of pain in this population have differed. Hadjimichael and colleagues have now performed a community-based study of the prevalence of pain in MS and its impact on patients' lives. Questionnaires asking about pain and uncomfortable sensations were mailed to the 18,725 participants in the North American Research Committee on MS Patient Registry. Of the 54% of patients who responded to the questionnaire, nearly 75% reported experiencing some pain in the previous month. The demographics and pain characteristics of those responding to the present survey were similar to those of non-responding patients in the Registry based upon earlier questionnaires.

Thirty-five percent of participants experienced mild to moderate pain (occasional or frequent pain that affects daily activities) and 13% had severe or totally disabling pain (daily pain that either necessitated a modification in or prevented daily activities). The most common sites of pain were the legs (30%), back (16%), feet (16%), arms (13%), head (12%), neck (10%), and face (3%). In addition, the quality of pain varied by body location — spasms were most common with leg pain, aching with back or neck pain, and tingling or burning with foot pain. Severe pain was more often reported by women and by individuals whose education was limited to high school. Pain severity strongly correlated with disability ($P < 0.0001$) as determined by a

patient self-report instrument, the Patient-Determined Disease Steps (*Mult Scler*. 1999;5:349-354.). It also correlated significantly with interference in daily life, including affects on mood, ability to walk or move about, sleep, work, enjoyment of recreational activities, and enjoyment of life in general (Medical Outcomes Study Pain Effects Scale). Other characteristics that were associated with severe pain were worsening MS symptoms over the past year, 4 or more body sites affected by pain, pain lasting more than 5 years, and constant pain. Multiple pain sites were the strongest predictor of pain severity upon stepwise regression analysis.

Individuals with severe pain were more likely to make healthcare visits (82% compared with 60% of those with mild pain). Neurologists were most often seen for pain-related symptoms, with 39% of those with mild pain, 43% with moderate pain, and 47% with severe pain seeking neurological care. Primary care physicians were the next most often visited (14% to 25%), followed by pain specialists (10%), physical therapists (8%), and psychologists (6%). Two-thirds of patients used medications for their pain, with 20% taking 3 or more drugs. Although over-the-counter drugs such as aspirin, ibuprofen, or acetaminophen were most commonly used, prescription analgesics (eg, opioids or anticonvulsants) were taken by 32% of individuals with mild pain, 39% with moderate pain, and 50% experiencing severe pain. Patients with severe pain rated the least satisfaction with their physicians' management of their pain, with 35% reporting dissatisfaction.

COMMENTARY

Lower extremity dysesthesias, backache, neuralgias, Lhermitte's symptom, and muscle spasms are common forms of pain in individuals with MS. Previous reports have estimated the prevalence of pain in MS patients to be 13% to 86%. The present study represents the largest community-based investigation to date and further highlights the significant impact of pain symptoms in patients with multiple sclerosis. Though pain strongly correlated with disability, the cross-sectional nature of the study's survey did not allow a causal relationship to be determined. However, the participants did acknowledge that pain interfered to a significant degree with their ability to move about, pursue recreations, and enjoy life.

Perhaps the most striking finding of this survey is the apparent underutilization of healthcare and medications by individuals with MS who experience pain. Only 3.6% of patients with moderate to severe pain had reported visiting a pain specialist. Indeed, fully 18% of those with severe pain had not sought any care at all. No explanation is given for this statistic, but one might speculate that some patients with severe pain had sought care and received treatment in the past without adequate relief of their symptoms, their negative experience thus discouraging them from seeking further care. The authors therefore encourage routine screening for pain in patients with MS as well as continuous reassessment. Numerous medications are available to treat pain and related symptoms in patients with MS (ie, non-opioid analgesics, opiates, muscle relaxants, anticonvulsants, antidepressants, and anxiolytics), as are a range of non-pharmacological treatments (eg, physical therapy, psychological counseling, biofeedback, massage therapy, and acupuncture). Given the varying nature of pain and the frequent co-existence of pain at more than one body site reported in this study, a multimodal approach to pain may well be warranted in many patients with MS. ■

Cardiac Valvular Disease Associated with the Dopamine Agonists Pergolide and Cabergoline

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD
Assistant Professor, Department of Neurology, Weill Medical College, Cornell University
Dr. Henchcliffe is on the speaker's bureau for GlaxoSmithKline, Teva/Eisai, and Boehringer Ingelheim.

Synopsis: *Two large independent studies raise further concern over increased risk of serious cardiac valve disease in patients treated for Parkinson's disease with ergoline dopamine agonists, pergolide and cabergoline.*

Sources: Schade R, et al. Dopamine Agonists and the Risk of Cardiac-Valve Regurgitation. *N Engl J Med*. 2007;356:29-38.

Zanettini R. et al. Valvular Heart Disease and the Use of Dopamine Agonists for Parkinson's Disease. *N Engl J Med*. 2007;356:39-46.

These 2 studies address concern over the likely association of cardiac valve disease with use of pergolide and cabergoline, dopamine agonists for symptomatic relief in Parkinson's disease and restless legs syndrome. Zanettini and colleagues used transthoracic echocardiography to determine the prevalence of cardiac valve regurgitation in 155 patients with Parkinson's disease, who had taken dopamine agonists for at least 12 months. Cases were compared with 90 age- and gender-matched controls. Those with known valvulopathy preceding agonist exposure, or prior use of ergot-derived drugs including anorectics were excluded. Mean patient age was 63.4 ± 9.2 years and 63% were male. Average daily drug doses were pergolide: 2.8 ± 1.2 mg; cabergoline: 3.6 ± 2.1 mg; pramipexole: 3.0 ± 1.1 mg; and ropinirole: 10 ± 3.3 mg. Clinically significant grade 3-4

regurgitation occurred more frequently in those taking pergolide (23%) and cabergoline (29%) than in those taking ropinirole or pramipexole (0%), or in control subjects (6%). Moreover, cumulative drug dose was higher in those with grade 3-4 regurgitation than those with grade 0-2 regurgitation.

Schade and colleagues examined a cohort of 11,417 subjects from the United Kingdom General Practice Research Database who were prescribed antiparkinsonian drugs between 1988-2005. Thirty-one cases were identified with new onset valve disease, and matched with 663 controls without valve disease but taking antiparkinsonian medications. For cases, mean age was 73.0 ± 7.8, 65% were male, 29 had Parkinson's disease, 3 had restless legs syndrome, and one had hyperprolactinemia. Exposure to pergolide and cabergoline was associated with increased rates of cardiac valve regurgitation, with adjusted incidence rate ratios of 7.1 (95% C.I. 2.3-22.3) and 4.9 (95% C.I. 1.5-15.6) respectively, with higher association in those exposed > 6 months or taking >3 mg daily of either drug. There was no association with use of either ropinirole or pramipexole.

COMMENTARY

Based upon a number of previous studies and case reports, pergolide carries a black-box warning regarding increased risk of cardiac valve disease, and recently a milder warning was issued for cabergoline. These 2 studies further support such concerns. Pergolide has been widely used for treatment of Parkinson's disease, and has also been studied in restless legs syndrome. Cabergoline is used in the United States to treat hyperprolactinemia, but is used in many countries as a long-acting dopamine agonist useful in Parkinson's disease treatment. Development of cardiac valve disease (fibrotic changes in valve leaflets), as well as pergolide-associated retroperitoneal and pleuropulmonary fibrosis, is thought to stem from activation of $5HT_{2B}$ receptors. It may thus stimulate mitogenesis via multiple pathways including Src kinase activation, potentially resulting in valvular "overgrowth" and hence regurgitation.[1] Pergolide and cabergoline are both potent agonists of $5HT_{2B}$ receptors, whereas other commonly used dopamine agonists do not possess significant $5HT_{2B}$ agonist activity. Accordingly, no association of cardiac valve disease with exposure to ropinirole and pramipexole was evident in these two studies. Given the alternatives now available in treatment of Parkinson's disease, it seems advisable to simply avoid the use of pergolide in Parkinson's disease. For patients who have been exposed, they should be counseled, undergo cardiac evaluation, and given the opportunity to switch medication. ■

Reference

1. Roth, BL. Drugs and Valvular Heart Disease. *N Engl J Med*. 2007;356:6-9.

Is Long-term Use of the Ketogenic Diet Safe and Effective?

ABSTRACT AND COMMENTARY

By John J. Caronna, MD

Vice-Chairman, Department of Neurology, Cornell University Medical Center, Professor of Clinical Neurology, New York-Presbyterian Hospital

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

Synopsis: *Patients treated with the ketogenic diet for more than 6 years showed sustained seizure reduction (90% decrease in seizure frequency) with few serious side effects.*

Source: Groesbeck DK, et al. Long-term use of the ketogenic diet in the treatment of epilepsy. *Developmental Medicine & Child Neurology*. 2006;48:978-981.

THE PURPOSE OF THIS STUDY WAS TO EVALUATE THE safety and efficacy of the ketogenic diet in the small fraction of patients who remain on the diet longer than the usual length of treatment (2-3 years). Patient records were retrospectively reviewed to identify patients who were started on the ketogenic diet between July 1993 and May 1999, and who remained on the diet for a continuous period of at least 6 years. Out of 386 patients who were started on the ketogenic diet, 28 patients were identified and were ages 7-23 years. The median time on the ketogenic diet was 7 years 9 months (range 6-12 years), median age at first seizure was 6 months, median age at diet onset was 3 years 9 months, median number of medications tried before diet onset was 5, and median seizure frequency per week at the start of the diet was 630 (range 1-1400). Of the 28 long-term patients, 24 experienced more than a 90% decrease in seizure frequency but only 3 achieved total seizure freedom. At diet onset, patients were on a median of 2 anticonvulsant medications (range 1-4) and at the most recent follow up or upon diet completion, the patients were on a median of one medication (range = 0-4); 9 patients were medication free.

At the time of records review, 19 patients were still on the diet. Compliance with the intricacies of the diet improved over time; however, many patients were fed by gastrostomy, which would eliminate some of the difficult aspects of the ketogenic diet, such as palatability and portion control. The diet was maintained on a long-term basis for these 28 patients because of sustained and dramatic seizure control, as well as concern by the families that changing to an antiepileptic medication would have more cognitive side effects than the diet. Many families resisted termination of the diet, even when the physician suggested doing so. Nine patients stopped the diet because of poor growth (2), seizure freedom (2), lack of benefit (2), restrictiveness (1), and death (1).

The authors investigated the various factors that might

affect seizure control and side effects and noted the following: 1) Severe vs mild ketosis did not affect seizure control ($P = 0.298$); 2) The diet had an adverse effect on long-term growth, both weight and height ($P = 0.011$); 3) There was an increased risk of developing kidney stones; 4) Fractures occurred frequently; 5) Dyslipidemia was an uncommon side effect and overall lipid profiles were within the normal range; 6) Liver function tests were unaffected; 7) Constipation was reported as a side effect of the diet in 15 patients; 8) The diet did not contribute to the death of the single patient who died while on the diet.

COMMENTARY

This retrospective chart review from Johns Hopkins reinforces our belief in the efficacy and safety of the ketogenic diet for patients with intractable seizures. The use of the ketogenic diet resulted in > 90% reduction of seizure frequency in 30-35% of children with intractable epilepsy. The long-term safety data presented here would suggest that for ketogenic diet responders, using the diet for more than 2-3 years is safe. More than half of the parents cited a side-effect profile for the ketogenic diet that was superior to medication, and this was their primary reason for staying on the diet. Most patients were on fewer medications after starting the diet and nearly a third were on no anticonvulsant medication at all.

However, continuous safety monitoring is imperative during the long-term use of the ketogenic diet. Physicians should monitor growth parameters closely. Due to the risk of developing kidney stones, prophylactic oral alkalinization, frequent monitoring for hematuria, and liberal fluid intake have been recommended for patients who are on the diet for prolonged periods of time. The high risk of fractures associated with the diet calls for vigilant monitoring of bone density and the administration of calcium and vitamin D supplements.

Because of the retrospective, self-report design of this study, confounding variables could be significant, such as the effects of cerebral palsy, developmental delays, anticonvulsant medications, and motor deficits that could independently contribute to growth delay, independent of the diet. The observed high rate of bone fractures and kidney stones may represent a selection bias as opposed to a true increase in incidence of these adverse effects. ■

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. ■

CME Question:

6. Binding of FDDNP, a PET radioligand, to the brain:
- A. reveals amyloid plaques but not neurofibrillary tangles
- B. Is increased in AD but not MCI
- C. Is highest in AD, lower in MCI and lowest in normals
- D. Is highest in normals, lower in MCI and lowest in AD

7. Exposure to which of the following drugs for Parkinson's disease is associated with an increased risk of cardiac valve disease?
- A. levodopa
- B. ropinirole
- C. rasagiline
- D. pergolide
- E. pramipexole

8. The most common site of pain in individuals with multiple sclerosis is
- A. the face.
- B. the back.
- C. the lower extremities.
- D. the neck.

9. Which of the following statements if false? Patients with PSS and neuropathy are likely to have:
- A. Subclinical demyelinating neuropathy
- B. Abnormally-increased F-wave latencies
- C. Mean IENF densities lower than normal
- D. Mean IENF densities lower than in SLE patients
- E. Mean IENF densities that are significantly less in the calf compared with the thigh

10. All of the following adverse effects are associated with the ketogenic diet except
- A. Bone fractures
- B. Hyperlipidemia
- C. Kidney stones
- D. Growth retardation
- E. Constipation

Answers: 6.(c) 7.(d) 8.(c) 9.(e) 10.(b)

In Future Issues:

LPa and the Risk of Stroke

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.

This Month's Issue Focuses on Women's Health

Breast Cancer Rates Have Dropped Since WHI of 2002

Several important papers have been published in the last 2 months, none more important than the realization that breast cancer rates have dropped precipitously since the publication of the Women's Health Initiative (WHI) in 2002. The issue of estrogen-alone (not in combination with a progestin) and the risk of breast cancer is addressed in a new paper, as is the use of herbal supplements to treat postmenopausal vasomotor symptoms in women who have stopped HRT. Finally the duration of treatment of bisphosphonates for osteoporosis gains some clarity with publication of new data from the Fracture Intervention Trial.

The WHI study of combined estrogen and progesterone was halted in 2002 when it was found that women on the drug combination were at increased risk of breast cancer. Prior to the publication of the study, it was estimated that 30% of American women over the age of 50 were taking HRT. Within 6 months of the publication of WHI, half of those women had discontinued HRT. Now preliminary data suggests that breast cancer rates dropped precipitously in 2003 compared to 2002. The decline was most pronounced in women over the age of 50, and the biggest decline was in estrogen-receptor-positive breast cancer. Breast cancer rates had been rising steadily in this country at an average of 1.7% per year until 1998 when the rate began declining at 1% per year. The 7% drop seen in 2003 was the largest single decrease ever seen within a single year. The data was presented at the 29th Annual San Antonio Breast Cancer Symposium by researchers from MD Anderson. In a separate study, researchers from Northern California presented their own data that showed a decrease in hormone use of 68% between 2001 and 2003, and a decrease in breast cancer rates of 10-11%, which was sustained to 2004 (*J Clin Oncology* 2006;24:e49-50). The implication is that the sudden decrease in HRT use is responsible for the decrease rate of breast cancer, a conclusion supported by the dramatic decrease in ER positive cancers in postmenopausal women.

In contrast to the findings of the estrogens/progesterone wing of the Women's Health Initiative, the estrogen-only wing showed no increased risk of breast cancer (*JAMA*. 2004;291:1701-12). This was in contrast to several European studies, including the Million Woman Study, which showed an increased rate of breast cancer with unopposed estrogen (*Lancet*. 2003;362:419-427). Now a new study also suggests that estrogen-only is associated with a slightly increased risk of breast cancer. The study from Finland looked at nearly 85,000 women using oral or transdermal estradiol, 8,000 women using oral estriol (widely used in Europe but uncommonly used in the United States), and 18,000 women using vaginal estrogens for least 6 months were followed from 1994 through 2001. There was no increase risk for breast cancer for estradiol use of less than 5 years. Women who used estradiol for more than 5 years had a relative risk of breast cancer of 1.44 (1.29-1.59). Oral and transdermal estradiol conveyed similar risk. Oral estriol and vaginal estrogens did not increase breast cancer risk. The authors con-

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.

clude that the use of estradiol for more than 5 years is associated with a increased risk of breast cancer (*Obstet and Gynecol*. 2006;108:1354-1360).

Herbal Supplements to Treat Vasomotor Symptoms

Many women who have stopped HRT have tried herbal supplements to treat vasomotor symptoms. A new study compares the effectiveness of black cohosh, multibotanicals, and soy with HRT and placebo. Researchers from the University of Washington enrolled 351 women who were in menopausal transition or were postmenopausal. They were given black cohosh 160 mg daily, multibotanical with black cohosh 200 mg plus 9 other ingredients, multibotanical plus dietary soy counseling, HRT with conjugated equine estrogen 0.625 mg daily with or without medroxyprogesterone 2.5 mg daily, or placebo. There was no difference in vasomotor symptoms between the herbal interventions and placebo at 3, 6, or 12 months or for the average over-all follow-up time points ($P > 0.05$ for all comparisons), with the exception that symptom intensity was significantly worse with the multibotanical plus soy compared with placebo ($P = 0.016$). Hormone therapy was effective at reducing vasomotor symptoms ($P < 0.001$). The authors conclude that black cohosh alone or as part of a multibotanical regimen was ineffective at treating menopausal vasomotor symptoms (*Ann Int Med*. 2006; 145: 869-879). As pointed out in an accompanying editorial, even though herbal supplements were found to be ineffective, the good news is that women in the placebo group had a 30% reduction in the severity and frequency of vasomotor symptoms during the 12-month follow up, a number that probably reflects the natural history of postmenopausal symptoms (*Ann Int Med*. 2006;145:924-925).

Bisphosphonates to Treat LBD, After 5 Years?

Since WHI, bisphosphonates have become the drugs of choice for many women with low bone density. Treatment with bisphosphonates for 5 years is safe and effective; however, treatment beyond 5 years has been debated with some experts recommending a "drug holiday" after 5 years because of a concern about diminished bone strength and microfractures. A new study suggests that there is no harm in extending treatment beyond 5 years, although there is minimal benefit. In the Fracture Intervention Trial (FIT), 1,099 postmenopausal women who had used alendronate for 5 years were randomized to 5 more years of alendronate 5 mg per day, 10 mg per day, or placebo. Outcomes were hip bone mineral density (BMD) with an exploratory outcome measure of fracture incidence. Compared to women who continued alendronate, those who were switched to placebo at 5 years had declines in BMD at the total hip (-2.4%; 95% CI, -2.9% to -1.8%; $P < 0.001$) and spine (-3.7%; 95% CI, -4.5% to -3.0%; $P < 0.001$). Still, despite discontinuing alendronate, BMD remained at levels above pretreatment levels 10 years earlier. The cumulative risk for non-vertebral fractures was not significantly different between those continuing or discontinuing alendronate (19% vs 18.9%). Those who continued alendronate had significant lower risk of clinically recognized vertebral fractures, however, (5.3% placebo vs 2.4% alendronate) but no significant reduction in morphometric vertebral fractures. Of the women continuing alendronate, 18 underwent bone biopsies and none showed any qualitative abnormalities. The authors conclude that discontinuing alendronate after 5 years results in a moderate decline in BMD, a gradual rise in biochemical markers, but no higher fracture risk other than for clinical vertebral fractures compared to women who continued alendronate. The data also suggests that stopping alendronate at 5 years is safe, although the authors suggest that high-risk women may want to continue beyond 5 years (*JAMA*. 2006;296:2947-2953). Interestingly, no cases of osteonecrosis of the jaw were reported in women who took alendronate for 10 years.

FDA Actions

The FDA has approved a new estradiol gel for the treatment of moderate to severe vasomotor symptoms assisted with menopause. The gel, which is applied daily, supplies the lowest dose of estradiol approved by the FDA for this indication. Estradiol gel will be marketed as "Elestrin" by Kenwood Therapeutics.

The FDA has approved Novartis' combination antihypertensive "Exforge." The drug combines valsartan and amlodipine in one pill that is dosed once daily. It is expected to be marketed by September 2007.

The FDA has approved the first generic ondansetron injection (Zofran) for the prophylaxis of postoperative nausea and vomiting, and nausea and vomiting associated with cancer chemotherapy. The generic is manufactured by Teva pharmaceuticals.

The FDA has also approved generic oxybutynin extended release tablets (Ditropan XL). 'The new generics will be available in 5 mg and 10 mg extended-release tablets made by Mylan, and 50 mg extended-release tablets manufactured by Impax Laboratories. Oxybutynin is indicated for once daily treatment of overactive bladder in patients with urge incontinence, urgency, and frequency.

A generic bupropion extended-release tablet has been approved by the FDA. The generic version of Wellbutrin XL for the treatment of depression will be available in 150 mg and 300 mg tablets. The new generic is manufactured by Anchen Pharmaceuticals. ■