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 E. 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.

Severe Symptomatic Carotid Artery Stenosis — Endarterectomy or Stenting?

ABSTRACT & COMMENTARY

By Philip E. Stieg, MD, PhD

Professor and Chairman, Department of Neurological Surgery, Weill Medical College of Cornell University; Neurosurgeon-In-Chief, New York Presbyterian Hospital

Dr. Stieg reports no financial relationships relevant to this field of study.

Synopsis: *The stroke and death rates at one and 6 months were lower in patients with symptomatic carotid stenosis (> 60%) treated with endarterectomy versus stenting.*

Source: Mas JL, et al. Endarterectomy versus stenting in patients with symptomatic severe carotid stenosis. *N Engl J Med*. 2006;355:1660-1671.

THE DEBATE REGARDING THE SUPERIORITY OR NON-INFERIORITY of carotid artery stenting performed with distal protection devices as compared to carotid endarterectomy (CEA) continues. This multi-centered, randomized, non-inferiority trial performed at 20 academic and 10 non-academic institutions in France compared the 30-day and 6 month outcomes in patients after carotid endarterectomy or stenting procedures with (> 60%) symptomatic stenosis of their carotid arteries.

The study enrolled patients from November 2000 until September 2005, but was terminated by the Safety Monitoring Committee due to safety and futility issues. A total of 527 patients were randomized into the trial. The primary endpoint was any stroke or death at 30 days; however, data was also collected at 6 months after the procedure was performed. Eligible vascular surgeons had to perform 25 endarterectomies in the previous year and interventional physicians had to perform at least 12 carotid stents or 35 total stents in the supraaortic trunk with at least 5 in the carotid arteries. However, interventional physicians with less endovascular experience could be tutored and mentored through the process. Physician outcome or complication history was not part of the selection criteria for treatment centers. Carotid stenosis was assessed by either duplex Doppler

VOLUME 25 • NUMBER 4 • DECEMBER 2006 • PAGES 25-32

NOW AVAILABLE ONLINE
www.ahcmedia.com

studies and MR angiography or catheter angiography alone. Exclusion criteria included the presence of critical tandem lesions in the carotid territories. Distal protection devices were applied midway through the study. All patients were assessed independently by neurologists, both before and after a procedure was performed.

The 30-day incidence of any stroke or death was 3.9% for CEA and 9.6% for stenting with a relative risk for stenting of 2.5 (95% CI = 2.0 to 7.2). The absolute risk increase was 5.7% for stenting compared to CEA. The 30-day disabling stroke and death rate was 1.5% for CEA and 3.4% for stenting with a relative risk for stenting of 2.2 (95% CI – 0.7 to 7.2). At 6 months, the incidence of any stroke or death was 6.1% in CEA patients and 11.7% of stenting patients. There were more local complications after stenting and more systemic complications after carotid endarterectomy. There were also more cranial nerve injuries after carotid endarterectomy. Of particular note, the cerebral protection device did lower the 30-day incidence of stroke or death from 25% to 7.9%, highlighting its importance. Dual or single anti-platelet therapy after stenting did not significantly impact the results. The mean hospital stay was 3 days after carotid stenting and 4 days after carotid endarterectomy.

COMMENTARY

The debate regarding superiority or non-inferiority of carotid artery stenting with distal protection devices versus carotid endarterectomy is still open. However, this trial clearly supports the advantages of carotid endarterectomy. The trial might have been slightly biased in favor of surgeons given the more stringent entry criteria for that group. However, the authors note that the number of procedures performed by a center and the number of procedures performed by an endovascular physician did not appear to have an influence on their outcomes. This trial, which did not select high-surgical-risk patients, failed to show a difference in myocardial infarction rate between the 2 groups. The impact of distal protection devices is very clear with a 17.1% reduction in stroke and death in the stent group that used distal protection. Moreover, it is unclear to this author what anti-platelet regimen was used in the stent group, and it appeared to vary between institutions. This may have had an influence on the 30-day stroke outcomes. Patient selection and technology will be important issues in future studies.

Careful review of this study and comparison to previous trials regarding carotid stenting versus CEA would lead this author to suggest that the only current indication for carotid stenting is a symptomatic patient with severe stenosis (> 70%) who is a high surgical risk. However, one must also be quite specific about "high surgical risk." At our institution, this would be limited to patients that have severe coronary artery disease who could not tolerate elevations in their systolic blood pressure to 180. ■

Neurology Alert, ISSN 0741-4234, is published monthly by AHC Media LLC, 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: 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: leslie.hamlin@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.

AHC Media LLC

Questions & Comments
Please call **Jennifer Corbett**, Associate Managing Editor, at (404) 262-5431.

HRT — It Can Increase Seizure Frequency in Postmenopausal Women with Epilepsy

ABSTRACT AND COMMENTARY

By Cynthia L. Harden, MD
Associate Professor, Neurology and Neurosciences, Weill Cornell Medical Center, Cornell University
Dr. Harden does research for Schwarz, GlaxoSmithKline, UCB, Ortho, and Ivax, is a consultant for Cyberonics and GlaxoSmithKline, and is on the speaker's bureau for Cyberonics, GlaxoSmithKline, UCB, Novartis, Pfizer, and Ortho.

Synopsis: *This randomized, double-blind, placebo-controlled study showed that standard hormone replacement therapy using Prempro can increase seizure frequency in postmenopausal women with epilepsy in a dose-related manner.*

Source: Hormone Replacement Therapy in Women with Epilepsy: A Randomized, Double-Blind, Placebo-Controlled Study. Cynthia L. Harden, et al. *Epilepsia*. 2006;47(9):1447-51.

THIS STUDY IS THE FIRST AND LIKELY SHALL BE THE only report in which Prempro is studied for its effects on brain excitability in women. The study was undertaken based on results of a survey in which postmenopausal

women with epilepsy reported on the course of their seizure disorder during life changes,[1] and almost incidentally, they reported that hormone replacement therapy (HRT) was associated with seizure exacerbation. This interesting result prompted further exploration of the effect of HRT on seizure frequency. It was especially provocative since estrogen has long been reported as neuroexcitatory and proconvulsant in animal models, leading to the question of whether the neuroactivity of exogenous estrogen could be adverse in women with epilepsy. Further, postmenopausal women, who have a stable reproductive hormonal milieu, are ideal subjects with which to test this hypothesis compared to women of reproductive potential who have monthly estrogen and progesterone surges.

The study herein used a single dose or a double dose of Prempro, which is 0.625 mg of conjugated equine estrogens plus 2.5 mg of medroxyprogesterone acetate or CEE/MPA, and compared it to placebo for an effect on seizure worsening. Both doses of Prempro were in common use at the time this study began, making this study of imminent practical relevance. Subjects underwent a 3-month baseline observation period, followed by a 3-month treatment period. Seizure outcome was analyzed simply by comparing the proportion of women whose seizure frequency increased with those whose seizure frequency did not increase. Women enrolled in this study generally had very stable epilepsy with infrequent seizures, which reflects the general population of persons with epilepsy. Although the enrollment of the study was limited due to the growing unpopularity of HRT, which reached its culmination with the WHI[2] results showing an increased risk of breast cancer, the authors were able to show an adverse effect on seizure frequency with the small numbers of subjects in the study.

COMMENTARY

These results indicate that in addition to other risks now shown with Prempro, there is a risk of seizure increase when it is used in postmenopausal women with epilepsy. Women with epilepsy will need to use HRT for relief of postmenopausal symptoms however, and sleeplessness due to "hot flashes" could also be a strong precipitant of increased seizure frequency. What can women with epilepsy use for short-term relief of menopausal symptoms?

It is possible that at least part of the risk shown in this study is due to the special components of Prempro, which is a mixture of estrogens present in pregnant mare's urine, and consists largely of estrone, with small components of the most potent estrogen, 17-beta estradiol, and other estrogenic molecules. Further, the progestin in Prempro is a powerful synthetic progestogenic molecule, medroxyprogesterone acetate. Rodent studies of the effects of hormones on brain excitability show that surges in 17-beta estradiol increase seizure activity; almost nothing is known about the effects of medroxyprogesterone acetate on neurophysiology.

Therefore, although an adverse effect on seizures was shown using Prempro in women with epilepsy, it is possible that low and stable doses of a more simplified regimen, such as 17 beta estradiol only with natural progesterone, which in and of itself has anticonvulsant properties in animal models,[3] may be safer for short term use in women with epilepsy. It should be emphasized that this study evaluated only one HRT regimen, albeit the most widely used one at the time. The use of another form of HRT, especially at lower doses, may be without this risk. The best advice from the author of this study is that women with epilepsy who need HRT for symptom relief could be treated carefully and cautiously with such a regimen. ■

References

1. Harden CL, Pulver MC, Jacobs AR. The effect of menopause and perimenopause on the course of epilepsy. *Epilepsia* 1999:40(10):1402-1407.
2. The Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy post-postmenopausal women: Principle results of the Women's Health Initiative randomized, controlled trial. *JAMA*. 2002;288:321-333.
3. Herzog AG. Progesterone therapy in women with epilepsy: a 3-year follow-up. *Neurology*. 1999;52(9):1917-8.

High-Dose Cyclophosphamide in MS

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: *A single, high-dose treatment of cyclophosphamide stabilized or improved function in multiple sclerosis patients with moderate to severe disease that did not respond to prior trials of immunomodulatory or immunosuppressive drugs.*

Source: Gladstone DE, et al. High-dose cyclophosphamide for moderate to severe refractory multiple sclerosis. *Arch Neurol*. 2006; 63:1388-1393.

GLADSTONE AND COLLEAGUES EVALUATED THE EFFICACY of high-dose cyclophosphamide (HDC) treat-

ment in 13 patients with moderate to severe relapsing-remitting (RRMS) or secondary progressive multiple sclerosis (SPMS). All patients in the study had had at least 2 relapses or suffered neurological deterioration during the previous year. In addition, all patients had been treated earlier with corticosteroids and interferon (IFN)-beta. Eleven patients also received a second IFN-beta formulation, glatiramer acetate (GA), IVIg, mitoxantrone, and/or another immunosuppressive therapy during the course of their disease. Except for steroids, these other therapies were stopped at least 3 weeks before the study began.

The patients received a total of 200 mg/kg of cyclophosphamide over 4 days. They also received mesna and forced diuresis to help prevent hemorrhagic cystitis as well as prophylaxis against bacterial, viral, and fungal infections. On day 10, patients began receiving granulocyte colony-stimulating factor (filgrastim) until their neutrophil counts reached 1000/mm^3. Blood or platelets were transfused at predetermined thresholds. Patients had repeated neurological, neuro-ophthalmic, and MRI examinations over 2 years.

Six patients had RRMS and 7 had SPMS. Their ages ranged from 26 to 52 years (median 41) and disease duration from 3.1 to 29 years (median 6.5). All but one subject was female. The level of disability on the Expanded Disability Status Scale (EDSS) for patients at study entry ranged from 4.0 (ie, relatively severe disability, but still fully ambulatory) to 8.0 (ie, retains most self-care functions, but largely restricted to bed or wheelchair). Patients were followed for 6 to 24 months (median 15). Of the 12 patients that could be evaluated clinically, 5 experienced at least a 1.0-point improvement on the EDSS, one had a 0.5-point improvement, 5 remained stable, and one worsened by 0.5 point. The results on the individual functional subscores that make up the EDSS were more variable, with most patients experiencing improvement in 2 or more functions and worsening in one or more. Of note, all patients had bladder dysfunction prior to treatment and 75% experienced improvement with HDC, with 50% experiencing a complete resolution of symptoms.

There were no significant changes in the number of T2-weighted lesions on brain MRI with treatment. Only 2 patients had gadolinium-enhancing lesions prior to treatment and only one developed an enhancing lesion after HDC. Visual acuity improved by 2 or more lines on the Snellen eye chart in 44% of patients. All patients reported an improvement in their quality of life and 88% reported a reduction in fatigue.

Patients tolerated the treatment well. On average, the subjects developed absolute neutropenia for 9 days and received one unit of packed red cells and one unit of platelets during treatment. Half the patients had neutropenic fever and most experienced nausea, but no long-term morbidity was observed.

COMMENTARY

Since its first use in a patient with multiple sclerosis (MS) 40 years ago, more than 30 clinical studies have examined the effects of cyclophosphamide on the disease. Upon review, Weiner and Cohen concluded that cyclophosphamide appears to be most effective in "cases of worsening MS that have an inflammatory component as evidenced by relapses and/or gadolinium-enhancing lesions on MRI or in patients in earlier stages of disease where inflammation predominates."[1] Consistent with this conclusion, the best responses to HDC (changes in EDSS scores from 5.5 to 2.0 and from 6.0 to 1.0) were seen in patients who had the shortest disease durations in the study (3.1 and 5.8 years, respectively), had 2–3 relapses in the previous year, and who had received no other treatments other than steroids and IFN-beta.

With traditional protocols, most treating neurologists administer cyclophosphamide at doses of 800-1000 mg/m^2 on a monthly or bimonthly basis for one to 2 years. This dose translates to 1.2–1.75 g/dose of cyclophosphamide for the average female patient. In contrast, the HDC in the present study would represent 11–13 g for a 55–65 kg woman. The HDC used by Gladstone et al is believed to eliminate the T cells and B cells that contribute to autoimmune diseases while sparing hematopoietic stem cells. As a consequence, the patients in this study required prolonged hospitalization, antimicrobials, and, in most cases, supportive transfusions of blood components while erythrocytes, white blood cells, and platelets were reconstituted. These considerations, as well as the toxic effects of cyclophosphamide, which include alopecia, infertility, and hemorrhagic cystitis, would thus limit the high-dose regimen to a selected subgroup of patients.

The design of this study makes it difficult to evaluate the efficacy of HDC compared to conventional cyclophosphamide protocols or to mitoxantrone, the only cytotoxic drug approved by the FDA for patients with worsening RRMS or SPMS. Post-treatment data were only provided for one patient who had previously received cyclophosphamide, and she demonstrated no change in EDSS score after HDC. Seven patients in the study had previously received mitoxantrone, but all had received submaximal doses. Nevertheless, this group of patients had stable or improved EDSS scores for a median of 16.5 months. It would be interesting to study HDC head-to-head with conventional cyclophosphamide protocols or mitoxantrone in patients with worsening RRMS or SPMS who have

already been treated with IFN-beta or GA.

In addition, a longer-term study should address the duration of the effects of HDC. Worldwide experience in over a hundred patients who have received autologous hematopoietic stem cell transplants (HSCT) for MS (some of whom were treated with HDC combined with another cytotoxic therapy) indicates that MS disease activity can resume after a few years in up to 40% of cases, despite this extreme treatment protocol. Indeed, even in the present study, there was MRI evidence of recurrent disease after HDC in one patient. Approximately 5% mortality has been observed with HSCT; therefore, it will be important to assess the risk of HDC in a larger cohort. A longer post-treatment observation period is also required with these patients before the long-term benefits of HDC can be determined. ■

Reference:

1. Weiner HL, Cohen JA. Treatment of multiple sclerosis with cyclophosphamide: critical review of clinical and immunologic effects. *Multiple Sclerosis.* 2002;8:142-154.

TIA Management: Emphasis on Urgent Evaluation and Treatment

ABSTRACT & COMMENTARY

By Dana Leifer, MD

Associate Professor, Neurology, Weill Medical College, Cornell University

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

Synopsis: *Patients with transient ischemic attacks should usually be admitted to the hospital and receive rapid evaluation and treatment.*

Source: Johnston, SC, et al. National Stroke Association Guidelines for the Management of Transient Ischemic Attacks. *Ann Neurol*. 2006:60:301-313.

A GROWING BODY OF EVIDENCE INDICATES THAT there is a significant risk of stroke in the days immediately after a transient ischemic attack. Johnston et al found that 5% of TIA patients had a stroke within 48 hours and another 5% had a stroke within 90 days. Several other groups have obtained similar results. In addition, Rothwell et al showed that approximately 20% of stroke patients have a TIA before their stroke and that of these, 26% occurred on the day of the stroke or the day before the stroke, and an additional 19% occurred between 2 and 7 days before the stroke (*Neurology*. 2005;64:817-820). Taken together, these data indicate a need to take TIAs seriously, to initiate appropriate preventive treatment quickly, and to facilitate rapid intervention if a stroke develops.

In this background, the National Stroke Association (NSA) established an expert panel to develop guidelines for TIA management. The panel was chosen objectively on the basis of publications related to TIA and stroke. After a literature search, the quality of evidence was rated, and recommendations were derived from the rated evidence. Multiple rounds of comments from the panel were used to derive a consensus, and panel members were excluded from contributing to topics for which they had a possible conflict of interest. This approach was designed to avoid bias in selection of experts, to prevent overweighting of dominant personalities in the consensus process, and to permit efficient updating of the recommendations.

The guidelines emphasize the need for timely treatment of TIAs. The chief points are: (1) Hospitalization should be considered for all patients presenting within 48 hours of their first TIA to facilitate thrombolytic therapy if a stroke develops and to begin secondary prevention rapidly. An important corollary that the guidelines do not address, however, is that if patients are admitted, they need to be monitored closely to minimize the delay in recognizing in-hospital strokes. (2) Timely referral to a hospital is also advisable for all patients within one week of a TIA and hospital admission is generally recommended for patients with crescendo TIAs, TIAs lasting more than one hour, > 50% carotid stenosis if symptomatic, known cardioembolic sources, known hypercoagulability, and combinations of other factors placing patients at high risk based on recently developed scales for rating stroke risk after TIA (*Stroke*. 2006;37:320-322).

The guidelines also make recommendations about the infrastructure that should be available for evaluation of TIA patients: (1) Local protocols should be established to identify patients who will be admitted and those who will be referred for outpatient evaluation. Specialty clinics for outpatient evaluation within 24 to 48 hours should be available for patients who are not admitted. Patients who are not admitted should be instructed to return at once if they have recurrent symptoms. (2) Patients not admitted should have access within 12 hours to CT or MRI, EKG, and carotid Doppler. These should be done within 24 to 48 hours if they are not done in an emergency room. If they are done and are normal, a longer period of up to 7 days may be appropriate for further work-up. (3) Patients with TIA within 2 weeks who are not admitted should be worked

up within 24 to 48 hours (ie, carotid Doppler, blood work, cardiac evaluation such as EKG, rhythm strips, and echocardiography). (4) Medical assessment should at least include EKG, CBC, electrolytes, creatinine, glucose, and lipid studies. (5) Imaging should include CT or MRI for all patients to rule out structural lesions such as acute stroke, subdural hemorrhage, and brain tumor (25% or more of patients with a clinical TIA may actually have had a small stroke). Some form of vascular imaging (ie, ultrasound, CTA, or MRA) should also be performed. Catheter angiography remains the gold standard, but should be used for diagnostic purposes primarily when the other tests are discordant or cannot be performed. (6) Cardiac evaluation with transthoracic or transesophageal echocardiography and testing for right to left shunting is advised in patients under 45 years of age if other studies do not identify a cause for the TIA.

The guidelines go on to make specific recommendation for antithrombotic therapy and for treatment of other specific risk factors that are identified during the work-up. These are important and emphasize the need for antiplatelet therapy for most patients, anticoagulation when indicated, and aggressive management of risk factors including carotid stenosis, hypertension, hyperlipidemia, and diabetes. The recommendations are largely similar to those of the American Heart Association's 2006 statement on stroke prevention (*Stroke*. 2006;37:577-617). Those guidelines, however, did not address the importance of rapid evaluation of TIA patients. The main importance of the new NSA guidelines is that they stress the need for rapid evaluation and treatment of TIA patients. ■

Dementia in Celiac Disease

ABSTRACT & COMMENTARY

By Gunnar Gouras, MD

Associate Professor of Neurology and Neuroscience, Weill Medical College, Cornell University

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

Synopsis: *Clinical-pathological study of patients with onset of dementia within 2 years of gastrointestinal symptom onset in Celiac disease.*

Source: Hu WT et al. Cognitive Impairment and Celiac Disease. *Arch Neurol*. 2006;63:1440-1446.

An association between celiac disease (CD) and cognitive decline has been described mainly in case reports; therefore, the 13 patients identified by Hu and colleagues from the medical records of the Mayo Clinic between 1970 and 2005 represent the largest study on CD and dementia. The authors provide comprehensive clinical-pathological descriptions of these 13 patients who were selected because they both had intestinal biopsy confirmed CD and developed dementia within 2 years of the onset of gastrointestinal symptoms (median age at onset 64; range 45–79). Ataxia was the most common additional neurological symptom seen in 10 of the patients; 2 patients had dementia as their only neurological symptom.

Remarkably, patients had an insidious subacute onset of cognitive decline with scores on cognitive testing consistent with moderate dementia. Indeed, 3 patients were given a diagnosis of possible Creutzfeldt-Jakob disease (CJD) because of initially rapid onset of dementia in association with ataxia, with 2 of 3 cases also having myoclonus and seizures. CJD was subsequently ruled out by neuropathological examination. Amnesia, acalculia, confusion, and personality changes were the most common initial cognitive features. The investigators noted that patients with onset of cognitive impairment within the first year after onset of GI symptoms had lower average cognitive scores than those with onset of cognitive decline in the second year. Neuropathological studies were carried out in 5 of 13 patients and showed non-specific gliosis, although one patient had ubiquitin-positive inclusions consistent with frontotemporal lobar degeneration with ubiquitin-only immunoreactive changes; the authors speculated that this might have been coincidence. Focal or generalized slowing was seen in 6 of 9 patients who had an EEG. The most common MRI abnormalities among the 7 patients who had brain MRIs were generalized atrophy (6 patients); frontal atrophy was seen in the remaining patient). Nonspecific scattered or confluent white matter T2 hyperintensities on MRI were also common.

The authors discuss the possible pathophysiological cause of this association, supporting an autoimmune mechanism in CD-associated dementia, analogous to CD-associated ataxia. The possibility of nutritional deficiency in CD is discussed, although the authors point out that in the 6 patients found to have reduced vitamin B12, folate or vitamin E, subsequent supplementation and normalization did not lead to cognitive improvement.

■ COMMENTARY

Finding additional causes of dementia and awareness of neurological symptoms associated with systemic diseases are important. Neurological symptoms are estimated to occur in about 10% of patients with celiac disease. Although ataxia and peripheral neuropathy are the

most frequently described neurological symptoms, cognitive dysfunction needs to be considered.

Caveats in interpreting this interesting study linking dementia to CD include that 13 patients is still a small number. It is also not fully clear when cognitive testing was performed and how much progression there was in the cognitive decline of these patients. Encouraging improvement or stabilization with a gluten-free diet was noted in 3 of the patients in this study, although more information on the adherence to a gluten-free diet among all the patients studied might have been helpful. The authors justifiably argue that the association between CD and cognitive impairment is unlikely only due to chance, especially since onset of GI and neurological symptoms occurred simultaneously in 5 patients. Further studies on this interesting association will be necessary. ■

Parkinson's Disease with Camptocormia: A Central or Peripheral Etiology?

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: *Camptocormia in PD is an extreme forward flexion of the spine, and has many characteristics of an axial action dystonia. The contribution of myopathy in muscles responsible for trunk extension has yet to be determined, and may be secondary to the dystonia itself.*

Sources: Bloch F et al. Parkinson's disease with camptocormia. *J Neurol Neurosurg Psychiatry*. 2006;77:1223; Lepoutre A-C et al. A specific pattern of camptocormia in Parkinson's disease. *J Neurol Neurosurg Psychiatry*. 2006;77:1229

In the first of two complementary studies, Bloch and colleagues identified 35 individuals with Parkinson's disease (PD) and camptocormia (defined as thoracolumbar anteroflexion 15°–90° standing or walking, disappearing when recumbent). Of these, 17 were studied in detail (exclusion criteria were known myopathy, dystonic syndrome, spinal cord disease, amyotrophic lateral sclerosis, spinal surgery, probable multiple system atrophy, and dementia). Mean age was 69.3 ± 7.2 years, 6/17 were women, mean disease duration was 12.2 ± 6.9 years, mean "off" Hoehn & Yahr score was 3.3 ± 0.9, and mean levodopa equivalent was 985 ± 535 mg/day. Spinal curvature responded poorly to levodopa (20%). Eight patients with PD but without camptocormia were compared, matched for age, disease duration, and Hoehn & Yahr score. Motor disability, as measured by the Unified Parkinson's Disease Rating Scale Part III, was worse "on" medication in subjects with camptocormia (24.7 ± 11.5 vs 13.3 ± 6.1, $P < 0.05$) but similar "off" medication. Similarly, axial motor scores were worse "on" medication for those with camptocormia (8.1 ± 2.6 vs 3.7 ± 1.5, $P < 0.05$), with more severe dysarthria, neck rigidity, gait, and postural instability. Interestingly, electro-oculographic recordings demonstrated abnormal horizontal gaze velocities in 28% of those with camptocormia, but in none of those without camptocormia. Electromyography failed to reveal evidence of myopathy in any. In the accompanying article, Lepoutre and colleagues examined 23 PD patients with camptocormia (defined as a totally or partially reducible forward flexion). Of the 23, 8 were women, mean age was 68.6 ± 7.4 years, mean disease duration was 10.3 ± 5.1 years, and onset was tremor-predominant in 12 vs akinetic-rigid in 13. MRI revealed abnormal signal in the thoracolumbar paraspinal muscles in 5/23 (non-specific in 2, and abnormally high signal on T2-weighted, fat-suppressed STIR sequence in 3). Myopathic changes were observed by electromyography in 3. Biopsy demonstrated focal paravertebral myositis (n = 1), type II fiber atrophy (n = 1), and fibrosis with fatty infiltration (n = 1).

COMMENTARY

Camptocormia, or "bent spine syndrome" is a poorly understood but debilitating and sometimes painful axial feature of PD.[1] It also occurs in a variety of other disorders, including dystonia and ALS. Reports of camptocormia due to focal lesions of the striatum and pallidum suggest a central etiology, but it has also been associated with myositis, prompting a debate regarding relative importance of central vs peripheral (ie, muscle) etiologies. Although the present studies do not provide a definitive answer to this debate, they do suggest how the two processes might interrelate in development of camptocormia. The authors found that the presence of camptocormia in PD is associated with older age, male gender, longer disease duration, abnormal electro-oculographic studies in some, and autonomic features; therefore, it may represent a distinct clinical subtype. Its poor response to dopaminergic agents in general (in common with other axial features) is suggestive of neurodegeneration in non-dopaminergic pathways, either within the basal gan-

glia or other sites such as the brainstem. In fact, Lepoutre and colleagues suggest that organizational changes in the corticospinal and reticulospinal tracts might be responsible for axial rigidity, leading to underactivity of truncal extension muscles, and, thus, secondarily to muscle atrophy. The present rigorously conducted studies represent a focused attempt to discern what characteristics might be associated with camptocormia, and one suspects that in the final analysis it may turn out that multiple underlying mechanisms are responsible. ■

Reference

1. Azher SN and Jankovic J Camptocormia: Pathogenesis, classification, and response to therapy. *Neurology*. 2005;65:355-359

CME Questions

23. Camptocormia as a symptom of Parkinson's disease is generally associated with:
a. a good response to levodopa
b. young-onset PD
c. mutations in LRRK2
d. duration of disease
e. dementia

24. Clinical evidence suggests that cyclophosphamide treatment is effective in multiple sclerosis patients with any of the following characteristics EXCEPT:
a. relapses.
b. a primary progressive course.
c. early stage of disease.
d. gadolinium-enhancing lesions on MRI.

25. Patients with a TIA should be admitted to the hospital
a. To facilitate thrombolytic therapy if they have a stroke.
b. To start secondary preventive therapy quickly to prevent a stroke.
c. Both A and B.
d. Neither

26. The guidelines state that patients with a TIA may appropriately wait for 2 weeks for an outpatient work-up.
a. True.
b. False.

27. Approximately what percentage of TIA patients will have a stroke within 48 hours?
a. 0.1%.
b. 1%.
c. 5%.
d. 10%.

28. Neurological symptoms that have been associated with celiac disease include all of the following EXCEPT:
a. Peripheral neuropathy
b. Ataxia
c. Agraphia
d. Amnesia

29. Common clinical-pathological features of Celiac disease associated dementia include all of the following EXCEPT:
a. slowing on EEG
b. non-specific gliosis on neuropathology
c. non-specific T2-hyperintensities on MRI
d. improvement after correction of vitamin deficiencies

Answers: 23.(d) 24. (b) 25. (c) 26. (b) 27. (c) 28. (c) 29. (d)

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. ■

Announcement

The 12th Annual "Clinical Neurophysiology: Principles and Practice" December 27, 28, 29, 2006. New York City, Presented by the Cornell University Medical College Department of Neurology. Contact: Fatima Castro, Department of Neurology, The New York Hospital Cornell Medical Center, 525 East 68th Street, Rm. K-615, New York, NY 10021; Telephone (212) 746-2320; Fax (212) 746-8984. Email: frcastro@med.cornell.edu

The 3rd Annual Update Symposium on Clinical Neurology and Neurophysiology, Feb. 19-21, 2007, Tel Aviv, Israel. Presented by Weill Cornell University Medical College Department of Neurology and Tel Aviv Medical Center. Information:

www.neurophysiologysymposium.com ■

In Future Issues:

Antipsychotics for Alzheimer's Disease