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

Vestibular Neuritis and Bell's Palsy: Same Cause? Same Treatment?

ABSTRACTS & COMMENTARY

Synopsis: *Methylprednisolone significantly improves the recovery of peripheral vestibular function in patients with vestibular neuritis, whereas valacyclovir does not.*

Sources: Strupp M, et al. Methylprednisolone, Valacyclovir, or the Combination For Vestibular Neuritis. *N Engl J Med.* 2004;351:354-361; Johnson RT. Vestibular Neuritis, or Driving Dizzily Through Donegal. *N Engl J Med.* 2004;351:322-323; Gilden DH. Bell's Palsy. *N Engl J Med.* 2004; 351:1323-1331.

THE SYNDROME OF VERTIGO WITHOUT AUDITORY SYMPTOMS, vestibular neuritis, is thought to result from inflammation of the vestibular nerve from a viral cause. Two different modes of viral injury have been proposed: either primary infection by a variety of viruses, or activation of herpes simplex virus type 1 (HSV1), latent in vestibular ganglia. According to the latter theory, vestibular neuritis and Bell's palsy share the same pathogenesis. Therefore, Strupp and colleagues reasoned that corticosteroids, antiviral agents, or a combination of both might improve the outcome in patients with vestibular neuritis.

In a randomized trial, they assigned 141 patients with vestibular neuritis to treatment with placebo (n = 38), Methylprednisolone (35), Valacyclovir (33), and Methylprednisolone plus Valacyclovir (35). Vestibular function was determined by caloric irrigation within 3 days of onset of symptoms, and again 12 months later. The mean (+SD) improvement in peripheral vestibular function at 1-year follow-up was 40 ± 28 percentage points in the placebo group, and 62 ± 17 percentage points in the Methylprednisolone group. Analysis of variance showed a significant effect of Methylprednisolone ($P < 0.001$), but not of Valacyclovir. The combination of Methylprednisolone and Valacyclovir was not superior to corticosteroid monotherapy.

Strupp et al compared their results with meta-analyses of studies of treatment for Bell's palsy and the statement of The Quality Stan-

VOLUME 23 • NUMBER 3 • NOVEMBER 2004 • PAGES 17-24

dards Subcommittee of the American Academy of Neurology that early treatment with oral corticosteroids is probably effective in improving facial function outcomes in Bell's palsy, but that the addition of acyclovir to prednisone is only possibly effective.[1]

Gilden reviewed the evidence in support of medical and surgical treatments of Bell's palsy and has updated recommendations for treatment of patients within 2 to 14 days after onset of symptoms: oral prednisone 1 mg./kg combined with oral Valacyclovir (1g b.i.d.) or famcyclovir (750 mg. t.i.d.) for 7 days.

COMMENTARY

Although Strupp et al assumed that Bell's palsy and vestibular neuronitis share the same pathogenesis, activation of HSV 1 at the time of disease has not been documented in vestibular neuritis as it has in Bell's palsy. Furthermore, Strupp et al found that antiviral treatment alone was not better than placebo. Nevertheless, as noted by Johnson in his editorial comments, it may be that HSV 1 is not involved, or is only 1 of many causes of vestibular neuritis, so that any beneficial effects of Valacyclovir were so diluted as to be undetectable.

By documenting that treatment with corticosteroids during the acute phase of vestibular neuritis improved caloric responses 1 year later, Strupp et al have, at a stroke, changed clinical practice. Corticosteroids should and will become part of the standard treatment for vestibular neuritis. The place, if any, for antiviral drugs in acute vertigo remains uncertain, and should be the subject of further studies. —**JOHN J. CARONNA**

Reference

1. Grogan PM, et al. *Neurology.* 2001;56:830-836.

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.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
GST Registration Number: R128870672.
Periodicals postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 740059, Atlanta, GA 30374.

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

THOMSON™
AMERICAN HEALTH CONSULTANTS

Subscriber Information

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

Subscription Prices

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

Accreditation

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

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

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

Questions & Comments

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

Statement of Financial Disclosure

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

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

Carotid Endarterectomy vs Stenting: When Randomized Becomes a Dirty Word

ABSTRACT & COMMENTARY

Synopsis: *Among patients with severe carotid-artery stenosis and coexisting conditions, carotid stenting with the use of an emboli-protection device is not inferior to carotid endarterectomy.*

Source: Yadav JS, et al. The SAPPHIRE Investigators. Protected Carotid Artery Stenting vs Endarterectomy in High-Risk Patients. *N Engl J Med.* 2004;351:1493.

CAROTID ENDARTERECTOMY (CEA) IS THE STANDARD OF care for patients with symptomatic carotid stenosis of > 70% severity. In men, CEA may be considered for stenoses as mild as 50-69%. For asymptomatic patients with stenoses > 60%, CEA may also be advisable, but the benefits are less robust. It is on this backdrop, that an alternative therapy, carotid artery stenting (CAS) with distal embolic protection, enters into the clinical calculus. Very recently, on August 31, 2004, the first stent system for the carotid (Guidant Corp.) passed through FDA approval.

The Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial compared CAS with CEA in a group of patients with comorbid conditions putting them in a high-risk category. In fact, these patients would have been excluded from prior randomized studies comparing efficacy of CEA with best medical management. Many of these patients had clinically significant cardiac disease, contralateral carotid occlusion, or had restenosis following prior CEA. Of a total of 747 patients entered into the study, 413 were determined to be non-randomizable, and were treated with CEA or CAS at the discretion of their treating physicians. The vast majority of these (406) were determined to be poor surgical candidates, and

underwent CAS. The randomized cohort was therefore quite small, comprising the remaining 334 patients. These were equally divided between CEA and CAS. The goal of the trial was not to show that CAS was superior to CEA, but rather clinical equivalence or non-inferiority.

The primary end point was stroke, myocardial infarction, or death within 30 days, or stroke/death up to 1 year. There were 20 events in the CAS patients and 32 in the CEA group, a non-significant trend in favor of CAS. This finding established non-inferiority of CAS, when compared to CEA. With the inclusion of myocardial infarction up to 1 year (a secondary end point), the advantage of CAS reached statistical significance (12% for CAS vs 20% for CEA, *P* 0=.048). Peri-procedural complications, including stroke, within 30 days, were 4.4% among CAS patients and 9.9% among CEA patients (*P* = .09). The complication rate for CAS for these high-risk patients compares favorably to that of CEA in low-risk patients (3-6%).

Unfortunately, the SAPPHIRE study was terminated early when recruitment of patients slowed in the face of competition from non-randomized CAS registries. Had the study been taken to completion, the study may have been powered to show superiority of CAS over CEA, rather than merely non-inferiority.

COMMENTARY

Although controversial and only partially randomized, the SAPPHIRE study is the only existing direct comparison between CAS and CEA. In the aftermath of SAPPHIRE, a series of industry-sponsored trials, bearing catchy acronyms such as CABERNET, MAVERIC, and SECURITY, have focused on CAS alone, to the exclusion of CEA. With these studies, merely collections of cases rather than true science, CAS technology has continued to push ahead of the less sexy CEA procedure. Only the publicly funded CREST study (Carotid Revascularization Endarterectomy vs Stenting Trial), along with a similar European trial will offer an unbiased, randomized head-to-head comparison. Unfortunately, such trials can be a hard sell to patients, especially now that stents are FDA approved and readily available to patients and physicians outside the confines of research studies. In addition, CAS is a moving target. Today's stents are superior to those of yesterday, and the more advanced stents to come (eg, those eluting anti-fibrotic drugs) will not bear comparison to those of today. Surgical technique remains essentially static, while endovascular technology is ever changing. Coronary artery stents are dramatically reducing the indications for coronary artery bypass grafting. Similarly, for carotid artery stenting, the future is now, with or without randomized trials. —**ALAN Z. SEGAL**

Functional MRI (fMRI) as a Replacement for the Wada Test in Evaluating Memory Function?

ABSTRACT & COMMENTARY

Synopsis: *Although further technical improvements and prospective clinical validation are required, these results suggest that mesial temporal memory activation, detected by fMRI during complex visual scene encoding, correlates with post-surgical memory outcome, and supports the notion that this approach will ultimately contribute to patient management.*

Source: Rabin ML, et al. Functional MRI Predicts Post-Surgical Memory Following Temporal Lobectomy. *Brain.* 2004;127:2286-2298.

The intracarotid amobarital (or Wada) test has been used for over half a century to pre-operatively determine language laterality and to assess the risk of amnesia in pharmacologically refractory epilepsy patients being evaluated for temporal lobectomy (TLX). Ideally, injection of the ipsilateral carotid artery with amobarabital produces no memory deficit, while contralateral injection induces severe (but temporary) amnesia. Such a highly lateralizing Wada indicates that memory is subserved solely by the non-epileptogenic temporal lobe, and the patient is not at significant risk for developing a global memory deficit. Memory function is also modality-specific for either verbal or non-verbal memory. The neuropsychological testing battery administered during the Wada test uses different tasks to subdivide memory functions to predict whether removal of mesial temporal structures may be contraindicated because of significant verbal or non-verbal amnesia complicating TLX.

Rabin and colleagues provide important data to suggest that fMRI testing of visual memory correlates well with the results of Wada testing. Moreover, fMRI predicted post-operative visual memory deficit in patients going on to TLX (the true gold standard for both fMRI and Wada). The study enrolled 35 patients undergoing pre-surgical evaluation for epilepsy and 30 normals. All subjects underwent both fMRI and Wada during a complex scene encoding task. Encoding performance was assessed by follow-up recognition testing. Twenty-three patients who subsequently underwent TLX, completed the same task outside the scanner an average of 6.9 months post-operatively.

A region of interest (ROI) analysis was performed to quantify hippocampal (H) activation alone, with a separate ROI including hippocampus, parahippocampus, and fusiform gyrus (HPF). Asymmetry ratios (AR) were calculated for activation for each ROI as ipsilateral minus contralateral divided by ipsilateral plus contralateral. Normal subjects showed symmetrical AR for fMRI (mean = 0.02 for hippocampus and < 0.007 for HPF). For patients, AR correlated with Wada for HPF but not the smaller H ROI. In addition, ipsilateral HPF AR showed a significant inverse correlation with good post-TLX memory outcome (ie, the lower ipsilateral fMRI absolute activation, the better the memory outcome). Surprisingly, a statistically significant correlation did not exist between contralateral fMRI AR and post-operative memory outcome. Finally, AR differences in either H or HPF ROI activation did not show the same correlation between seizure outcome and Wada memory results as previously reported (*Neurology.* 1994;44:2322-2324 and *Epilepsia.* 1995;36:851-856).

COMMENTARY

Neurology Alert has previously (October 2002, p. 15 and August 2003, p. 92) commented upon the use of fMRI as a replacement for the Wada test and deficiencies related to inadequate memory testing paradigms as the reason why fMRI was not ready for prime time in this application. Gaillard and colleagues (*Neurology.* 2002;59:256-265) addressed the validity of fMRI for lateralizing language. Sabsevitz and colleagues (*Neurology.* 2003;60:1788-1792) looked at fMRI in conjunction with the Boston naming test to show that fMRI compares favorably with Wada in predicting verbal naming deficits following TLX. The current study by a collaborative group from the Thomas Jefferson University and the University of Pennsylvania convincingly demonstrates that fMRI can also predict post-TLX visual memory deficit in medically refractory epilepsy patients.

Over just a few years, it appears that fMRI has advanced almost to the point of a clinically relevant tool. Two key questions remain unanswered. First, can all 3 neuropsychological paradigms provide the same information in a single study session, as each has reported separately? There is no a prior reason to think otherwise. Second, can a combined verbal and nonverbal memory fMRI yield the same positive predictive information about seizure control following TLX as a highly lateralized Wada test can? The only data thus far available to answer this question are from Rabin et al, and these are unfortunately negative. —**ANDY DEAN**

A Major Advance in CT Angiography, Volumetric Computed Tomography (VCT)

ABSTRACT & COMMENTARY

Synopsis: *VCT substantially improves imaging of vascularization in tumors and offers a promising tool for preclinical studies of tumor angiogenesis and antiangiogenic therapies.*

Source: Kiessling F, et al. Volumetric Computed Tomography (VCT): A New Technology For Noninvasive, High-Resolution Monitoring of Tumor Angiogenesis. *Nature Med.* 2004; 10:1133-1137.

As mentioned in the most recent *Neurology Alert*, it is likely that advances in CT technology will lead to markedly enhanced ability to assess carotid vascular lesions, as well as small vessels in the brain. This may make it possible to non-invasively monitor cerebral aneurysms. This will be particularly valuable in ruling out mycotic aneurysms. It may also be possible to monitor perfusion in acute stroke to define areas at risk. A major advance in enhancing our ability to do this will be the development of volumetric computed tomography (VCT). This is an extremely high resolution CT scanner which has been recently developed by General Electric. The first report on utilizing this was just published. Detectors are used for imaging large volumes of a subject with isotropic imaging resolution. The prototype VCT scanner used flat-paneled X-ray detectors, and is designed for high-resolution 3-dimensional imaging.

In the present report, Kiessling and colleagues used this technique to study microangiography in xeno-transplanted skin squamous cell carcinomas in nude mice. VCT showed the vessel architecture of the tumors in animals with greater detail and plasticity than has previously been achieved. It was superior to contrast-enhanced magnetic resonance angiography. VCT, and MR images correlated well for larger tumor vessels. However, VCT was clearly superior for smaller vessels. It was demonstrated that it could detect small vessels with a diameter of approximately 30 microns. The scan is exceedingly fast. One scan was done in 16 seconds; an acceptable MR scan time was 28 minutes. Kiessling et al compared VCT and MRI for larger vessels of approximately 50 microns, and found that both techniques would visualize these. However, again the VCT

was more sensitive. VCT angiography was optimized using iodine-containing agents. They were able to image small vessel networks inside the tumor tissue, providing improved discrimination of vital and necrotic regions.

COMMENTARY

The development of VCT will provide an extremely advanced tool for imaging vascular lesions in the central nervous system. It will probably also lead to markedly improved identification of carotid artery stenosis. I believe it will also be useful for CT perfusion to identify the penumbra of acute strokes, which are areas that may be salvaged by interventional treatments. The VCT has resolution of 30-50 microns. This is an advance over conventional digital subtraction angiography, as well as MR angiography. It also has the advantage of extremely rapid scanning. —**M. FLINT BEAL**

Possible Role of Retroviral Gene Expression in Multiple Sclerosis

ABSTRACT & COMMENTARY

Synopsis: *Syncytin's proinflammatory properties in the nervous system demonstrate a novel role for an endogenous retrovirus protein, which may be a target for therapeutic intervention.*

Source: Anthony JM, et al. Human Endogenous Retrovirus Glycoprotein-Mediated Induction of Redox Reactants Causes Oligodendrocyte Death and Demyelination. *Nature Neurosci*. 2004;10:1088-1095.

ANTHONY AND COLLEAGUES STUDIED THE POTENTIAL role of human endogenous retrovirus (HERV) gene products in triggering the inflammatory, demyelinating pathology of multiple sclerosis. The HERV envelope glycoprotein syncytin was found to be upregulated in the brain tissue from 3 patients with multiple sclerosis, both at the mRNA and protein level, particularly in areas of active demyelination. Transfection and expression of the syncytin envelope gene in glial cell cultures was shown to induce the production of oxidant molecules (nitric oxide) and inflammatory cytokines (interleukin-1) that were toxic to oligodendroglial cells. Rodents that were similarly transfected with syncytin in the corpus callosum showed oligodendroglial cell loss and increased microglial cells with hypertrophic astrocytes. In this animal model, the rodents with histopathological changes had associated neurological motor deficits, both of which could be prevented by the anti-oxidant ferulic acid.

During primate evolution over a million years ago, retroviruses invaded the genome and integrated to now account for up to 8% of human DNA. Most of the retroviral sequences are not expressed. However, some of these HERV sequences have retained functional regulatory sequences and open reading frames for expression, and may have a role in normal human physiology and disease. Syncytin is a 518-amino acid membrane glycoprotein that is highly expressed in the placenta, where it is involved in trophoblast cell fusion and syncytium formation. Syncytin appears to bind to an amino acid transporter receptor that also serves as a retrovirus receptor. There is evidence that retroviruses in humans and other animals (eg, HIV, HTLV-I, and lentiviruses) exert a variety of neuropathological effects, some by direct neurotoxic effects of the envelope protein, or by inducing a secondary host inflammatory immune response. Anthony and colleagues have found an association between the inflammatory pathology in multiple sclerosis and the expression of syncytin in the brain, and have developed an interesting animal model of disease which supports a specific therapeutic strategy with antioxidants. However, the presence of syncytin could be an epiphenomenon of inflammation, just as inflammation may be inducing a number of proteins, as well as certain herpes viruses, such as HHV-6, that have been demonstrated in brain lesions of multiple sclerosis patients. Further studies are needed to determine if blocking syncytin controls the inflammatory reaction, or whether B or T cell immune reactivity against syncytin, occurs in multiple sclerosis. —**BRIAN R. APATOFF**

Neuropathy in Neurofibromatosis

ABSTRACT & COMMENTARY

Synopsis: *Peripheral neuropathy in NF-1 patients is a marker for poorer prognosis and mandates heightened vigilance for malignancy and spinal cord complications.*

Source: Drouet A, et al. Neurofibromatosis-Associated Neuropathies: A Reappraisal. *Brain.* 2004;127;1993-2009.

AMONG 688 NEUROFIBROMATOSIS TYPE-I (NF-I) patients followed in 2 NF clinics in France between 1995-2002 and satisfying established National Institutes

of Health (NIH) Consensus criteria for NF-1, 18 (2.3%) demonstrated diffuse peripheral neuropathy. None had diabetes, vasculitis, paraproteinemia, renal insufficiency, thyroidopathy, B12, folate deficiency, human immunodeficiency virus (HIV), hepatitis B or C virus, or Charcot Marie Tooth type 1. Of the 14 men and 4 women, 3 had severe, and 5 had moderate, sensorimotor neuropathy. Mild sensory neuropathy was present in 2, and 8 were minimally or non-symptomatic, and were diagnosed electrodiagnostically. All but 2 were chronic in nature. Seventy-seven percent (n = 14) demonstrated demyelinating neuropathy, half of which showed concomitant axonal changes, either severe (n = 3) or mild to moderate (n = 4). Four of the 18 patients had axonal neuropathy. Subcutaneous and large nerve root neurofibromas was strongly associated with peripheral neuropathy, and morbidity and mortality was much higher than expected in the NF-1 neuropathy patients, compared to the non-neuropathy group. Twenty-two percent (n = 4) developed a malignant peripheral nerve sheath tumor, and 2 died. Peripheral neuropathy in NF-1 patients is a marker for poorer prognosis, and mandates heightened vigilance for malignancy and spinal cord complications.

COMMENTARY

Tumor suppression appears to be the raison d'etre of the NF-1 gene. Neurofibromin, the 2818 amino acid protein product of this gene, shows a striking sequence similarity to the catalytic domain of proteins that negatively regulate Ras guanosine triphosphate (GTP)ase proteins (Arun D, et al. *Curr Opin Neurol.* 2004;17;101-105). Ras is an effective growth promoter, and loss of NF-1 gene function allows Ras activity to run amok, resulting in cell proliferation and tumorigenesis. NF-1 gene dysfunction also impairs cyclic adenosine monophosphate (cAMP) formation necessary for modulation of cell growth, suggesting another mechanism whereby the NF-1 mutation allows unbridled cell growth.

Neurofibromas are the most common tumor in NF-1 individuals, and up to 13% of patients develop malignant peripheral nerve sheath tumors. Significantly, these highly invasive and metastatic tumors have recently been shown to demonstrate an abnormal proliferation-promoting triad of NF-1 deletion, aberrant epidermal growth factor receptor expression, and homozygous p16 tumor suppression gene deletion.

Optic pathway gliomas are the 2nd most common NF-1 associated tumor, but are symptomatic in only a third. Typically arising in the optic nerve and chiasm, hypothalamus, brainstem, and cerebellum, their main management challenge remains how to predict which will need intervention and which will not. Annual ophthalmologic evaluation is recommended for all NF-1 children younger than 10 years of age. —**MICHAEL RUBIN**

How Do Mutations in DJ-1 Cause Parkinson's Disease?

ABSTRACTS & COMMENTARY

Synopsis: *Dopamine neurons derived from in vitro differentiated DJ-1 deficient embryonic stem cells showed decreased survival and increased sensitivity to oxidative stress.*

Sources: Shendelman, et al. DJ-1 Is a Redox-Dependent Molecular Chaperone That Inhibits a-Synuclein Aggregate Information. *PLoS Biology.* 2004;2(11):e362; Martinat, et al. Sensitivity To Oxidative Stress in DJ-1 Deficient Dopamine Neurons: An ES-Derived Cell Model of Primary Parkinsonism. *PLoS Biology.* 2004;2(11):e327.

PARKINSON'S DISEASE IS CHARACTERIZED BY DEGENERation of mid-brain dopaminergic neurons, leading to a progressive movement disorder. An autosomal recessive form of Parkinson's Disease was recently identified. This was caused by homozygous mutations in DJ-1 in 2 families. The mechanism by which DJ-1 produces Parkinson's Disease however, is as yet unknown.

In 2 recent papers published in a new freely available online journal, the mechanisms by which DJ-1 lesions produce Parkinson's Disease were evaluated. Interestingly, there appears to be a link between a chaperone function of DJ-1, as well as oxidative damage. DJ-1 was shown to function as a redox-sensitive molecular chaperone that is activated in an oxidative environment. The DJ-1 chaperone activity in vivo extends to alpha-synuclein, a protein implicated in autosomal dominant Parkinson's Disease.

In the accompanying paper, Shendelman and colleagues utilized a new technique to evaluate the function of DJ-1 in human dopaminergic embryonic stem cells. Human embryonic stem cells were cultured and differentiated into dopaminergic stem cells by culturing them on a glial stroma. Shendelman et al found that the embryonic stem cells deficient in DJ-1 display increased sensitivity to oxidative stress, as well as proteosomal inhibition. The accumulation of reactive oxygen species in toxin-treated DJ-1 deficient cells was initially normal, but they were unable to cope with the consequent damage, leading to apoptotic cell death. The cells were abnormally sensitive to 6-hydroxy-dopamine. Dopamine neurons derived from

in vitro differentiated DJ-1 deficient embryonic stem cells showed decreased survival and increased sensitivity to oxidative stress.

COMMENTARY

These 2 papers provide a mechanism by which DJ-1 mutations may cause Parkinson's Disease. They show that DJ-1 is important in protecting against oxidative damage. However, its primary effect is to act as a molecular chaperone. It therefore links oxidative damage to protein aggregation. It appears that DJ-1 normally functions in an oxidative stress environment to inhibit protein aggregation. As such, this protein links 2 fundamental processes which are implicated in Parkinson's Disease pathogenesis. —**M. FLINT BEAL**

Does Deep Brain Stimulation Improve Sexual Well-Being in Parkinson's Disease?

ABSTRACT & COMMENTARY

Synopsis: *Deep brain stimulation of the subthalamic nucleus appears to affect sexual functioning in a small but positive way. Male patients with Parkinson's Disease, especially when younger than 60, appeared more satisfied with their sexual well-being over a short-term follow-up period.*

Source: Castelli L, et al. Sexual Well-Being in Parkinsonian Patients After Deep Brain Stimulation of the Subthalamic Nucleus. *J Neurol Neurosurg Psychiatry*. 2004;75:1260-1264.

Sexual function in people with Parkinson's Disease (PD) is likely affected by a complex interplay of factors, including the disease itself, medication changes, and psychological and social effects. This report provides the first data concerning changes in sexual well-being in patients with advanced PD, after deep brain stimulation (DBS) targeting the subthalamic nucleus (STN). Improvements in motor function, as well as decreased medication requirements are well-documented results of this surgical intervention, but its effects on non-motor symptoms are less clear.[1] Castelli and colleagues investigated a group of 31 patients with PD, complicated by severe motor fluctuations and drug-related dyskinesias. Twenty-one of the 31 patients were male, mean age was 61.7 years, and mean disease duration was 16.9 years. Sexual function was evaluated with the sexual functioning inventory (SFI), a newly abbreviated form of the Gollombok Rust inventory of sexual satisfaction (GRISS). The full form was found to be unacceptable for those patients in the study. Depression and anxiety were also measured using the Beck Depression Inventory (BDI) and the State-Trait Anxiety Inventory (STAI-X1/X2). Subjects were interviewed 1 month prior to surgery, and 9-12 months after surgery. Total SFI scores were slightly lower after DBS in both men and women, but did not reach statistical significance. Analysis of subdomains revealed only 1 area of statistical significance: improvement in sexual dissatisfaction in male subjects. In the subgroup of men aged less than 60 years old (n = 7), improvements reached statistical significance in domains regarding infrequency of sexual intercourse, dissatisfaction, and avoidance. No correlation could be discerned between changes in sexual function and other variables, including Hoehn and Yahr stage, disease duration, or depression and anxiety.

COMMENTARY

This is the first report to systematically address the issue of whether STN DBS may influence sexual well-being in PD. Castelli et al are to be commended for initiating this study, in an area notoriously challenging in terms of methodology. Sexual dysfunction in PD is common, as highlighted by Brown and colleagues.[2] Despite its importance, there is scant, and sometimes conflicting, information concerning a complex relationship to disease severity and duration, associated autonomic dysfunction, depression, medication effects, and other factors such as hormonal changes, social, and cultural considerations. In this study, changes in SFI scores observed were positive, but for the most part small. It is tempting to ascribe any changes in sexual well-being to a non-specific consequence of overall improvement in physical function. No correlation between SFI score and Hoehn and Yahr stage of PD was revealed in this study, but scores reported do not take into account the full spectrum of severity of motor fluctuations and dyskinesias. Therefore, they may not reflect motor symptoms that interfere with sexual function, such as the degree of rigidity or abnormal involuntary movements. Overall, interpretation is limited given the small number of participants, along with use of a novel version of an established rating scale as primary outcome measure. Therefore, possible contributions of mood, medication reduction, and other factors influenced by DBS cannot be ruled out. Finally, little attention has been paid, to date, to effects of PD upon women's sexuality, although they clearly exist.[3] No significant improvement in women's sexual well-being was demonstrated, but again this may be due to small numbers involved and difficulties in data collection. This emphasizes the need

for further study of this complex area of patients' lives, and should encourage physicians to communicate with their patients about sexual function. —**CLAIRE HENCHCLIFFE**

Claire Henchcliffe, MD is an Assistant Professor of the Department of Neurology at the Weill Medical College of Cornell University, New York, NY.

References

1. Limousin P, et al. *N Engl J Med*. 1998;339:1105-1111.
2. Brown RG, et al. *J Neurol Neurosurg Psychiatry*. 1990;53:4810-4816.
3. Welsh M, et al. *Mov Disorders*. 1997;12:923-927.

CME Questions

15. Complications of neurofibromatosis type-1 (NF-1) include:

a. Optic nerve gliomas
b. Sensory neuropathy
c. Cerebellar gliomas
d. Malignant peripheral nerve sheath tumors
e. All the above

16. The study by Strupp et al indicated that the treatment of vestibular neuritis should include:

a. Intravenous corticosteroids
b. P.O. corticosteroids
c. Intravenous acyclovir
d. P.O. acyclovir
e. Surgical decompression of the vestibular portion of CN VIII

Answers: 15. (e); 16. (b)

Correction

The CME Questions in the October 2004 issue of *Neurology Alert* should have been numbered 12, 13, and 14 instead of 6, 7, and 8.

Readers are Invited

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

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Neurology Alert	0 7 4 1 - 4 2 3 4	10/1/04
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$319.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305
Contact Person: Robin Salet
Telephone: 404/262-5489

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*
3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*
Publisher *(Name and Complete Mailing Address)*
Brenda Mooney, 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305
Editor *(Name and Complete Mailing Address)*
Leslie Hamlin, same as above
Managing Editor *(Name and Complete Mailing Address)*
Glen Harris, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
Thomson American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Thomson Healthcare, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: Neurology Alert
14. Issue Date for Circulation Data Below: September 2004

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			1775	1665
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	1305	1256
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	9	8
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	77	74
	(4)	Other Classes Mailed Through the USPS	62	69
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			1453	1407
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	14	15
	(2)	In-County as Stated on Form 3541	2	2
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			25	25
f. Total Free Distribution *(Sum of 15d and 15e)*			41	42
g. Total Distribution *(Sum of 15c and 15f)*			1494	1449
h. Copies Not Distributed			281	216
i. Total *(Sum of 15g. and h.*			1775	1665
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			97	97

16. Publication of Statement of Ownership
Publication required. Will be printed in the November 2004 issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/27/04

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
2. In cases where the stockholder or security holder is a trustee, include in items 10 and 11 the name of the person or corporation for whom the trustee is acting. Also include the names and addresses of individuals who are stockholders who own or hold 1 percent or more of the total amount of bonds, mortgages, or other securities of the publishing corporation. In item 11, if none, check the box. Use blank sheets if more space is required.
3. Be sure to furnish all circulation information called for in item 15. Free circulation must be shown in items 15d, e, and f.
4. Item 15h., Copies not Distributed, must include (1) newsstand copies originally stated on Form 3541, and returned to the publisher, (2) estimated returns from news agents, and (3), copies for office use, leftovers, spoiled, and all other copies not distributed.
5. If the publication had Periodicals authorization as a general or requester publication, this Statement of Ownership, Management, and Circulation must be published; it must be printed in any issue in October or if the publication is not published during October, the first issue printed after October.
5. In item 16, indicate date of the issue in which this Statement of Ownership will be published.
6. Item 17 must be signed.

Failure to file or publish a statement of ownership may lead to suspension of second-class authorization.

PS Form **3526**, September 1999 *(Reverse)*

In Future Issues:

Leprosy and Neuropathy

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.*

The FDA and Merck Fielding Concerns About Vioxx

Merck announced on September 30th that it is voluntarily withdrawing rofecoxib (Vioxx) from the worldwide market. The decision was based on data from the APPROVe (Addenomatous Polyp Prevention on Vioxx) trial, a company sponsored perspective randomized, placebo-controlled trial designed to assess whether the drug reduces the risk of colorectal polyps in patients with a history of colorectal adenomas. However, after 18 months of the study, patients on 25 mg of rofecoxib were noted to have an increased risk of cardiovascular events such as myocardial infarction and stroke, compared to those patients taking placebo. The FDA supported Merck's action and acknowledged that, while the risk to any individual on rofecoxib is small, the risk increases with continued use. The APPROVe trial showed that the risk of cardiovascular events with rofecoxib was twice that of placebo, according to information published on the FDA News website (fda.gov/bbs/topics/news/2004/NEW01122.html). Previous studies, including a recently reported Kaiser Permanente/FDA retrospective trial, showed the risk to be 3 times that of placebo. The FDA is investigating whether cardiovascular risk may be a class effect of COX-2 inhibitors (coxibs), and is reviewing data from similar trials with celecoxib (Celebrex) and valdecoxib (Bextra). Meanwhile, Merck is initiating a buy-back program for unused Vioxx prescriptions, reimbursing patients for their unused prescriptions. The withdrawal has enormous implications for the company and its shareholders, not only from the loss of nearly $2 billion in revenues from drug, but lost share value for the company stock and the risk of future legal action. It is estimated that 2 million patients in the United States were taking Vioxx at the time of the withdrawal, and over 84 million people worldwide have taken drug at some point since its approval in May 1999. The October issue of the *New England Journal of Medicine* has 2 scathing reviews of Merck and the FDA with regard to the approval and marketing of rofecoxib. Dr. Eric Topol of The Cleveland Clinic, who was one of the first to raise concerned about rofecoxib, calls for a full Congressional review of this case. The senior executives at Merck, and the leadership of the FDA, share responsibility for not having taken appropriate action and not recognizing that they are accountable for the public health (*N Engl J Med.* 2004;351:1707-1709). Dr. Garrett FitzGerald of the University of Pennsylvania suggests evidence has been there all along that coxibs, including celecoxib and valdecoxib, may promote cardiovascular disease by blocking prostaglandin I2, which inhibits platelet aggregation, promotes vasodilation, and prevents the proliferation of vascular smooth muscle cells in vitro. At the same time, coxibs have little effect on thromboxane A2, which is responsible for platelet aggregation.

This supplement was written by William T. Elliott, MD, FACP, Chair, Formulary Committee, Kaiser Permanente, California Division; Assistant Clinical Professor of Medicine, University of California-San Francisco. In order to reveal any potential bias in this publication, we disclose that Dr. Elliott reports no consultant, stockholder, speaker's bureau, research, or other financial relationships with companies having ties to this field of study. Questions and comments, call: (404) 262-5416. E-mail: leslie.hamlin@ thomson.com.

Traditional NSAIDs and aspirin block thromboxane production, accounting for their cardioprotective effects. Dr. FitzGerald states, "It is essential to determine whether cardiovascular risk is or is not a class effect." The burden of proof now rests with those who claim that this is a problem for rofecoxib alone, and does not extend to other coxibs." (*N Engl J Med*. 2004;351:1709-1711).

Erythromycin and the Risk of Sudden Death

Erythromycin may be associated with an increased risk of sudden death, according to new study in the *New England Journal of Medicine*. Oral erythromycin, which is extensively metabolized by cytochrome P-450 3A (CYP3A), prolongs cardiac repolarization, and has been associated with reports of torsades de pointes. Commonly used medications that inhibit CYP3A may increase plasma erythromycin levels, increasing the risk of ventricular arrhythmias and sudden death. Researchers from Vanderbilt reviewed data from a Tennessee Medicaid cohort that included more than 1.2 million person-years of follow-up and 1476 confirmed cases of sudden death from cardiac causes. The patients in the study were relatively young, with a mean age of 45. Seventy percent were female, and 58% were white. The multivariate adjusted rate of sudden death from cardiac causes among patients using erythromycin was twice as high as that among those who had not used any of the study antibiotic medications (incident-rate ratio 2.01; 95% CI, 1.08-3.75; $P = 0.03$). There was no increase in sudden death among patients using amoxicillin, or former users of erythromycin. For patients who were taking erythromycin with concurrent use of a CYP3A inhibitor (nitroimadazole antifungal agent, diltiazem, verapamil, or troleandomycin), the adjusted rate of sudden death was 5 times as high (incident rate ratio 5.35; 95% CI, 1.72-16.64; $P = 0.004$). The authors conclude that erythromycin should be avoided in patients who are taking CYP3A inhibitors (*N Engl J Med.* 2004;351:1089-1096).

Vaccine Shortage Putting Americans At Risk

Just as healthcare providers are about to start their annual flu vaccination program, British regulators have shut down Chiron Corporation's Liverpool flu vaccine manufacturing plant due to sterility problems. Chiron was expected to supply nearly 50 million doses of vaccine this year, half of the hundred million doses health officials expected to be administered to Americans this fall. Aventis, the other major supplier of vaccine, has told health officials that he could produce an additional million doses this year, but no more. Compounding the shortage, is the addition of 2 groups of patients recommended to receive the vaccine this year—children between the ages of 6 and 23 months (who require 2 doses 1 month apart) and pregnant women (or women who anticipate being pregnant during the flu season). Other high-risk patients include people over age 65, people in nursing homes, people with chronic illnesses, and those caring for people in these groups. Healthcare workers are also considered the highest priority for vaccination. The nasal flu vaccine, FluMist, does little to alleviate the shortage since it is only indicated for healthy children and adults between the ages of 5 and 49 years.

FDA Actions

The FDA will move ahead with warnings for many antidepressants stating that the drugs sometimes raise the risk of suicidal behavior in youth. The recommendation comes after an agency advisory panel, on a split vote, recommended a Black box warning. The agency may not go that far, however, since some advisors were concerned that warnings may discourage treatment of depressed children and teens who can benefit from antidepressants medications. The drugs subject to the warning are those with the brand names Prozac, Paxil, Wellbutrin, Zoloft, Celexa, Effexor, Luvox, and Remeron.

The recently approved antidepressant duloxetine (Cymbalta) has received FDA approval for treatment of pain associated with diabetic neuropathy. This is the first drug approved for this indication in this country. In 2 studies submitted to the FDA, the drug reduced 24-hour average pain levels, compared with placebo, in patients who had diabetes for an average of 11 years, and had neuropathic pain for average of 4 years.

The FDA has approved a new extended release formulation of hydromorphone for the management of persistent moderate-to-severe pain in patients requiring continuous, round-the-clock opioid pain relief for extended periods of time. The product is an extended release formulation that can be dosed once a day, and will be available in 12, 16, 24, and 32 mg capsules. The drug is only recommended for patients already receiving opioid therapy who have demonstrated opioid tolerance, and who require a minimum total daily opioid dose equivalent to 12 mg of oral hydromorphone. It will be marketed by Purdue pharmaceuticals with the trade name Palladone.