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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.

Deep Brain Stimulation for Parkinson's Disease: A Randomized, Controlled Study Answers Many Remaining Questions

ABSTRACT & COMMENTARY

By Michael G. Kaplitt, MD, PhD

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

Synopsis: *Deep brain stimulation significantly increases "on" time, reduces dyskinesias, reduces "off" time, and improves various quality-of-life measures compared with best medical therapy in patients with moderate to advanced Parkinson's disease.*

Source: Weaver FM, Follett K, Stern M, et al. Bilateral deep brain stimulation vs. best medical therapy for patients with advanced Parkinson's disease: A randomized controlled trial. *JAMA* 2009;301:63-73.

DEEP BRAIN STIMULATION (DBS) FOR PARKINSON'S DISEASE (PD) HAS been approved in the United States and other countries for nearly a decade, and has clearly benefited thousands of patients who develop motor fluctuations, resistant tremors, increasing "off" times, and/or dyskinesias following years of medical therapy. Despite this long experience, however, many practitioners who manage PD patients remain unclear as to the role of DBS in the management of this disorder due to the surprising lack of large, well-controlled, and well-designed studies evaluating the true benefits and risks of this procedure in a diverse patient population.

Recently, a large, multicenter, randomized, controlled trial comparing DBS with best medical therapy clarified many of these residual questions. A consortium of Veterans Affairs and university hospitals randomized 255 patients with idiopathic PD to DBS (n=121) or best medical therapy (134). Patients were at least Hoehn and Yahr stage 2 or greater off medication, had poorly controlled motor symptoms ("off") for at least three hours per day, had disabling symptoms despite ongoing medication

VOLUME 27 • NUMBER 8 • APRIL 2009 • PAGES 56-63

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(such as severe motor fluctuations or adverse effects such as dyskinesias), and did not have significant medical contraindications for surgery, dementia, or prior surgical interventions. Outcomes were assessed by a rater blinded to treatment, and patients were additionally randomized based upon age, as this study uniquely included a fairly large number (25%) of patients older than 70 years.

The most striking findings of this study were the substantial improvements in most standard motor measures six months following DBS, with virtually no changes in the best medical therapy group. "On" time without disabling dyskinesias increased in the DBS group from 6.4 to 10.9 hours per day ($p<0.001$). This is even more impressive when considering that the average sleep time in both groups remained relative stable over time, at roughly seven hours per night, indicating that DBS improved good "on" time from 38% percent of waking hours to nearly 65% of waking hours following surgery. The improvement was due to both a decrease in the number of hours "on" with disabling dyskinesias as well as a decrease in the amount of "off" time. Similarly, the off-medication motor scores improved by nearly 30%, which is a bit lower than some earlier open-label studies but was still substantially greater than in the best medical group, which improved only 4% ($p<0.001$). Activities of daily living and several other quality-of-life measures also significantly improved in the DBS group, with no change in the best medical group, reflecting the genuine benefit that patients derived from these objective motor changes.

As with any therapy involving surgery and implants, several adverse events were observed which have long been familiar to DBS practitioners. A single patient died from a serious intracerebral hemorrhage following surgery, while 12 patients (10%) developed infections that required removal of all or part of the DBS system, and eight patients experienced hardware malfunctions or lead migrations. Surprisingly, the rate of adverse events was no greater in the group older than 70 years of age compared with younger patients, while the motor outcomes were also similar between groups, suggesting that properly chosen older patients can derive equivalent benefit with no greater risk than younger patients.

■ COMMENTARY

While DBS has been subjected to a variety of small studies as well as evaluations of patients on and off stimulation, the absence of large, randomized studies has somewhat restrained patient referrals due to ongoing confusion as to which patients should undergo surgery and what benefit can they expect to achieve. The current results build upon an earlier report by a European consortium which was the first large. randomized study comparing DBS and best medical therapy.[1] Similar benefits of DBS were reported there again with no further benefit of best medical therapy and with a similar adverse-event profile. That was a smaller study (155 patients) and all patients were younger than 75 years old. The current report now adds a second major study to the literature, which confirms the longstanding belief that DBS, in the properly chosen patient, can provide significant improvements in motor function and quality of life with an acceptable adverse event profile given the level of presurgical disability.

A particularly important finding in the current study is the lack of differences in both benefits and adverse events following surgery in older (>70) patients compared with younger patients. It has long been believed, based upon anecdotal observations, that older patients have higher complications and less improvement following DBS. Since PD is a disease of aging, and with improvements in general health of the population over the past 40 years, the current result refutes that belief and suggests that withholding surgery based solely upon age is not justified and that this procedure should be considered for a larger group of patients in need. It is also interesting that best medical therapy by very experienced experts in PD management resulted in no change in any major motor parameters over time. This suggests that patients with sufficient disability after many years of good response to medication are unlikely to derive substantial benefit from delaying surgery for incremental changes in medications.

Certainly any surgical therapy must be carefully considered on an individual basis, and there were adverse events unique to the surgical group that were not surpris-

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

ASSOCIATE PUBLISHER: Coles McKagen.
MANAGING EDITOR: Allison Weaver
DIRECTOR OF MARKETING: Schandale Kornegay

GST Registration Number: R128870672.
Periodicals Postage Paid at Atlanta, GA 30304 and at additional mailing offices.

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.

AHC Media LLC

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Questions & Comments

Please email **Allison Weaver**, Managing Editor, at allison.weaver@ahcmedia.com.

ing. All surgeons in this study were highly experienced and all used stereotactic frames and microelectrode recording, so these results cannot determine if other methodologies or differing levels of surgical experience influence outcomes. Longer-term follow-up is also needed to determine the stability of DBS effects, which have been anecdotally believed to be stable over several years, but which has never been formally studied in such a large patient population. Weaver and colleagues confirm that DBS, performed by experienced practitioners using this methodology, can substantially benefit patients who have responded well to medical therapy in the past but who now have significant motor fluctuations, "off" time, and/or disabling dyskinesias, and do not have significant medical or neurocognitive deficits regardless of age. Combined with the earlier report, this study should increase confidence in the value of DBS for this patient population and should be seriously considered when symptoms responsive to DBS become difficult to manage medically and significantly impair the quality of life.

Reference

1. Deuschl G, Schade-Brittinger C, Krack P, et al. A randomized trial of deep-brain stimulation for Parkinson's disease. *N Engl J Med* 2006;355:896-908. ■

Natural Anti-amyloid Autoantibodies in Alzheimer's Disease

ABSTRACT & COMMENTARY

By Norman Relkin, MD, PhD

Director, Memory Disorders Program, and Associate Professor of Clinical Neurology, Weill Cornell Medical College.

Dr. Relkin reports that he receives grant/research support from Baxter Bioscience, and is a consultant to Eisai, Pfizer, Myriad, and Smart Genetics. Dr. Relkin also reports he is leading a Phase 3 clinical trial of Intravenous Immunoglobulin for treatment for Alzheimer's disease, funded by the National Institute on Aging and Baxter Healthcare.

Synopsis: *The spontaneous development of anti-amyloid antibodies may have an impact on the development of plaques and Alzheimer's disease.*

Source: Kellner A, Matschke J, Bernreuther C, et al. Autoantibodies against beta-amyloid are common in Alzheimer's disease and help control plaque burden. *Ann Neurol* 2009;65:24-31.

AUTOANTIBODIES AGAINST BETA AMYLOID ARE COMMON in the blood of Alzheimer's disease (AD) patients and may play a role in controlling the density of neuritic plaques in the brain, according to a recently published study. Dr. Kellner of the University Hospital in Hamburg, working with colleagues in Switzerland and Spain, developed a tissue microarray (TMA) platform to quantitatively examine brain tissue from 48 autopsy-proven AD patients and an equal number of elderly controls. The TMA platform enables quantitative measures of parameters such as plaque burden, microglial activation, and microhemorrhage to be carried out on serial brain sections.

The study showed that the majority of neuritic plaques in AD patients in areas such as the entorhinal cortex were decorated with IgG autoantibodies. The degree of staining differed across AD patients. When the investigators divided the cohort into low versus high IgG-staining subjects, an interesting relationship became apparent. AD patients with higher levels of IgG binding had less amyloid burden in their brain. There was no increase in microhemorrhage in the high IgG group, which is a notable positive in that microhemorrhage has been a side effect of certain anti-amyloid immunotherapies in recent AD clinical trials. The study also confirmed that immune activation in the form of activated and phagocytic microglial cells is common in the AD brain. More phagocytic microglia were found in the brains of AD patients with high IgG binding.

In another set of experiments, the investigators took serum from eight AD patients and studied the binding of autoantibodies to brain tissue obtained from a transgenic mouse model of AD. They divided the patients' serum into high and low binding groups based on the degree to which they stained amyloid plaques in the mouse brains. Once again, patients with serum that exhibited high binding to the mouse brain had lower plaque burden at autopsy. The difference in amyloid burden was most apparent for diffuse plaques, which were relatively increased in the low plaque binding group.

Based upon these studies, the authors concluded that naturally occurring anti-amyloid autoantibodies may help to maintain amyloid homeostasis in the brain. If so, such antibodies may be relevant to the pathophysiology and potentially the treatment of Alzheimer's disease.

■ COMMENTARY

Several past studies have shown that autoantibodies against the beta amyloid molecule are present in the blood of normal individuals as well as patients with Alzheimer's disease. The physiologic relevance of the antibodies has been questioned. Their titers are relatively low compared to antibodies that are induced by anti-amyloid vaccina-

tion. This is not unexpected, since beta amyloid is a physiologic peptide that is present throughout life. Recent evidence has emerged that special classes of conformation-selective antibodies against beta amyloid aggregates are also present in blood, and bind to oligomeric and fibrillar forms of beta amyloid. Such antibodies could well account for the staining observed in the Kellner study.

The finding that anti-amyloid IgG binding is inversely correlated with plaque burden in AD is encouraging evidence that naturally occurring antibodies are involved in the body's innate defenses against proteins that undergo misfolding such as beta-amyloid. The value of such antibodies for the treatment of AD is currently being tested in multicenter AD studies of intravenous immunoglobulin, a polyclonal mixture of human antibodies that contains significant anti-amyloid activity. ■

Functional Recovery Despite Status Epilepticus in Post-Anoxic Coma

ABSTRACT & COMMENTARY

By Nicholas D. Schiff, MD

Associate Professor of Neurology and Neuroscience, Center for the Advanced Study of Brain Injury, Weill Cornell Medical College

Dr. Schiff reports that he receives grant and research support and is a retained consultant for Intelect Medical, Inc.; and is an inventor of patented technology through Cornell.

Synopsis: *Postanoxic status epilepticus does not necessarily imply irreversible and fatal brain injury.*

Source: Rossetti AO, Oddo M, Liaudet L, et al. Predictors of awakening from postanoxic status epilepticus after therapeutic hypothermia. *Neurology* 2009;72:744-749.

COMA FOLLOWING CARDIAC ARREST GENERALLY CARries a grave prognosis and a majority of patients will not survive or recover function above the level of vegetative state.[1] A new report by Rosetti and colleagues importantly emphasizes that prognosis in coma may be uncertain even in circumstances that appear to strongly predict poor outcome following cardiac arrest. The investigators report on a small cohort of six patients treated with hypothermia who recovered consciousness with varying degrees of functional recovery despite the presence of post-anoxic status epilepticus (PSE).

PSE is a clinical indicator positively associated with poor outcome in anoxic coma and often used to limit aggressive care in the early stages of treatment following cardiac arrest. All patients in the Rosetti study received mild hypothermia (external cooling to 33° C) for 24 hours with passive rewarming over 6–12 hours. Intact brainstem reflexes were present within 36 hours for all patients (measured off sedation with core temperature greater than 35 °C), but motor response was inconsistent. The EEG in all six patients showed background activity and reactivity (using the gross measures of a 10 microvolt amplitude threshold and any identifiable change with external stimulation). Additionally, somatosensory evoked potential (SSEP) measurements obtained from five of the patients showed intact cortical responses. Functional recovery at six months for the cohort ranged from full recovery and return to work (1), moderate disability (3), to severe disability (2). One patient remained in a minimally conscious state at 18 days after arrest prior to death from multi-organ failure.

The six patients in this observational study were drawn from two groups, one studied retrospectively (three patients from a group of 107 patients) and another prospectively (three patients from a group of 74 patients). Collectively, the subjects represented about 10% of all patients with PSE in both groups. The majority of patients studied prospectively with electroclinical myoclonic PSE (23/24) did not awaken, whereas two of four patients with only EEG evidence of PSE recovered (a statistically significant difference).

The authors cite prior series reported in the literature of patients with status epilepticus and myoclonus following cardiac arrest that found small numbers of patients showing significant improvements. In case reports of patients similar to those discussed by Rosetti and colleagues who achieved good recovery despite PSE, brainstem function also remained intact.[2,3] Collectively, the current and earlier studies support the conclusion that if indicators of preserved neuronal integrity (such as brainstem reflexes, EEG activity/reactivity and SSEPs) are present, PSE should be aggressively treated. Although electroclinical PSE carried a very poor prognosis in their overall study, the dissociation of clinical and electrical evidence of functional preservation is clearly important and demonstrates the limitations of using PSE a proxy for neuronal death following anoxic injury.

■ COMMENTARY

From this report it is not clear whether hypothermia changed the underlying distribution of patients with PSE who show clinical indicators of preserved neuronal function. Nonetheless, the application of new interventions, particularly the increasingly widespread use of hypothermia, is likely to change current outcome predictors. To

date, strong prospective negative indicators in the setting of anoxic/hypoxic-ischemic encephalopathy have been based on early clinical assessments and are well correlated with natural history and anatomic pathology.[4,5] While existing measures do not reflect the potential impact of interventions such as hypothermia to alter the natural history of recovery, the present report suggests that these traditional indirect measures from clinical evaluation and electrical assessments will continue to be important indicators. Based on the findings of Rosetti, clinicians should consider the evaluation of prognosis of coma following cardiac arrest in the context of treatments received and track clinical examinations closely. Moreover, the report suggests avoiding the summary withdrawal of care based on single factors such as PSE as a guide to outcomes of vegetative state or death. As more aggressive therapeutic interventions are applied early, this approach will become increasingly unreliable.

References

1. Booth CM, Boone RH, Tomlinson G, et al. Is this patient dead, vegetative, or severely neurologically impaired? Assessing outcome for comatose survivors of cardiac arrest. *JAMA* 2004;291:870-879.
2. Golby A, McGuire D, Bayne L. Unexpected recovery from anoxic-ischemic coma. *Neurology* 1995;45:1629-1630.
3. Goh WC, Heath PD, Ellis SJ, et al. Neurological outcome prediction in a cardiorespiratory arrest survivor. *Br J Anaesth* 2002;88:719-722.
4. Adams JH, Graham DI, Jennett B. The neuropathology of the vegetative state after acute insult. *Brain* 2000;123:1327-1338.
5. Posner J, Saper C, Schiff N, et al. *Plum and Posner's Diagnosis of Stupor and Coma* (4th Ed.). New York; Oxford University Press: 2007. ■

Lean, Lanky, Smoky, Headachy: At Risk of Cervical Artery Dissection?

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD

Associate Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Jamieson reports she is a retained consultant for Boehringer Ingelheim, Merck, and Ortho-McNeil, and is on the speaker's bureau for Boehringer Ingelheim and Merck.

Synopsis: *Risk factors for spontaneous dissection of carotid and vertebral arteries include smoking, migraine, and a tall, thin body. Women are at increased risk of dissecting multiple arteries.*

Sources: Metso TM, Metso AJ, Salonen O, et al. Adult cervicocerebral artery dissection: a single-center study of 301 Finnish patients. *Eur J Neurol* 2009;Feb 9. [Epub ahead of print]; Arnold M, Pannier B, Chabriat H, et al. Vascular risk factors and morphometric data in cervical artery dissection: A case-control study. *J Neurol Neurosurg Psychiatry* 2009;80:232-234; Arnold M, De Marchis GM, Stapf C, et al. Triple and quadruple spontaneous cervical artery dissection: Presenting characteristics and long-term outcome. *J Neurol Neurosurg Psychiatry* 2009;80:171-174; Metso AJ, Tatlisumak T. Cervical artery dissections: Multiple dissections and morphometric data. *J Neurol Neurosurg Psychiatry* 2009;80:130.

As non-invasive techniques for imaging neck vessels improve, spontaneous cervicocephalic artery dissection (sCAD) is more commonly diagnosed in adults, with or without ischemic stroke. Two recently published retrospective studies assessed the risk factors, comorbidity, and prognostic factors in patients with dissection of the cervicocranial carotid and vertebral arteries.

Metso and colleagues conducted a hospital-based analysis of 301 consecutive Finnish adults with sCAD. Two thirds of the patients were men (68%). Women were younger than men. Migraine (36% of all patients), especially with aura (63% of all migraineurs), and smoking were more common in patients with sCAD than in the general Finnish population. More than 80% of patients had a favorable outcome at three months. Occlusion of the dissected artery, internal carotid artery dissection, and recent infection were associated with a poorer outcome. Seven (2.3%) patients died during the follow-up (mean 4.0 years, 1,186 patient years). Known dissection recurrence was found in only 2% of patients.

In a case-control study by Arnold and colleagues, the major vascular risk factors—body weight, body height, and body mass index (BMI)—of 239 French patients with sCAD, obtained from a prospective hospital-based registry, were compared with 516 matched healthy controls. The mean body height was higher in sCAD patients than in controls (171.3 [SD 8.6] cm vs 167.7 [8.9] cm; $p<0.0001$) and sCAD patients had a significantly lower mean body weight (67.5 [12.2] kg vs 69.3 [14.6] kg; $p<0.001$) and mean BMI (22.9 [3.3] kg/m^2 vs 24.5 [4.2] kg/m^2; $p<0.0001$) than controls. The overall frequency of hypertension, diabetes, smoking, and dyslipidemia did not differ significantly between sCAD patients and controls. Migraine prevalence was not assessed. Only two patients in the study were found to have a connective tissue disorder.

While sCAD of more than two cervical arteries is rare, multiple cervical vessels can dissect simultaneously. Arnold and colleagues found that of 740 consecutive patients with sCAD, 11 (1.5%) had three, and one had four (0.1%) sCAD, none of whom had evidence of an underlying arteriopathy. Eight of 12 patients were women, consistent with prior data that women are more likely to have multiple dissections. Mirroring the results in the Finnish study, current smoking was noted in five of the 12 French patients and migraine was noted in half. Multiple sCADs caused clinical symptoms and signs mainly in one vascular territory, with most patients having a favorable outcome. Minor trauma or prior infection was associated with multiple dissections.

■ **COMMENTARY**

Dissection of the arteries in the neck is a recognized cause of ischemic stroke in younger patients without traditional vascular risk factors. While some causes of arterial dissection are associated with recognized trauma, most cases appear unrelated to any overt episode of abnormal neck positioning or movement. Two large studies of patients with sCAD reveal risk factors of smoking, migraine and an ectomorphic body type. Smoking and migraine were also risk factors for the simultaneous dissection of multiple arteries. The association between migraine with aura and arterial dissection is particularly intriguing, adding to the possible explanations for the link between migraine with aura and ischemic stroke. While the association with smoking may relate to chronic endothelial damage, correlation with migraine is perplexing. A transient vasculopathy has been suggested as a possible mechanism for multiple sCADs; however, these studies of patients with sCAD did not find an association with an underlying arteriopathy or with traditional vascular risk factors. Metso and Tatlisumak point out in their accompanying editorial that we know relatively little about the pathophysiology or the optimal treatment for sCAD. Ongoing research, such as the Cervical Artery Dissection and Ischemic Stroke Patients consortium and the British trial randomizing patients to antiplatelet or anticoagulant therapy, the Cervical Artery Dissection in Stroke Study, may provide useful information on prevention and treatment. ■

Rituximab for Myasthenia

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, Weill Cornell Medical College

Dr. Rubin reports that he receives grant/research support from Pfizer and is on the speaker's bureau of Athena Diagnostics.

Synopsis: *The monoclonal antibody, rituximab, appears to benefit patients with myasthenia gravis that is refractory to other modalities.*

Source: Lebrun C, Bourg V, Tieulie N, et al. Successful treatment of refractory generalized myasthenia gravis with rituximab. *Eur J Neurol* 2009;16;246-250.

WHAT CAN YOU OFFER A PATIENT WITH REFRACTORY generalized myasthenia gravis (MG) after he or she has failed plasma exchange, intravenous immunoglobulin (IVIG), and immunosuppressive therapy? Rituximab may be an option. Six MG patients who responded poorly to thymectomy followed by subsequent immunosuppression with at least two different drugs (corticosteroids, azathioprine, intravenous cyclophosphamide, cyclosporine, or mycophenolate mofetil) received rituximab intravenously. Refractory MG was defined as no symptomatic improvement within six months, with patients requiring over 360 mg of cholinesterase inhibitors daily, and IVIG infusion resulting in no additional improvement. Four were male, all were bedridden, ages ranged from 27 to 78 years, and only one was anti-acetylcholine receptor antibody positive. Anti-MuSK (muscle-specific receptor tyrosine kinase) antibodies were present in three others. Diagnosis in the seronegative patients was made by clinical presentation, decremental response on repetitive nerve stimulation, and positive prostigmine test. Rituximab infusion was given at lymphoma doses, 375 mg/m^2 weekly for the first month, followed by a single dose every two months thereafter, subject to clinical response.

Improvement was evident by the end of the first month of treatment, with all patients requiring reduced dosage of anti-cholinesterase medication and demonstrating clinical improvement as indicated by their Osserman score. Subsequent infusion frequency was determined by clinical course and was administered when patients felt a need for increased anti-cholinesterase medication. Two patients each required infusion for one and two years. By one year following treatment induction, five patients were no longer receiving steroid medication, the single exception being a patient who also suffered from Crohn's disease. Maximum anti-cholinesterase dosage was 180 mg/day. Adverse events, including significant infection and hematologic or metabolic toxicity, were not seen, and rituximab was well tolerated. Acute gout was precipitated in one patient with hyperuricemia, and transient worsening of diabetes and hypertension was seen in another. Rituximab appears to be beneficial and safe for refractory generalized MG.

■ **COMMENTARY**

Monoclonal antibodies, as a therapeutic modality, are the new frontier in medicine. Rituximab, developed by recombinant DNA technology using human and murine genes, is a chimeric IgG1 monoclonal antibody against the B-lymphocyte antigen CD20, beneficial in the treatment of autoimmune disorders, including myasthenia gravis (MG), and neoplastic diseases, including B-cell non-Hodgkin's lymphoma and B-cell leukemia. T cells play a role in the development of MG and antibodies (basiliximab) directed against CD25, expressed on activated T and B cells, may also be beneficial in MG.[1] Administered intravenously and intermittently over nine months in a patient with severe MG, moderate improvement was achieved, allowing withdrawal of steroid medication. However, repeated bacterial infections including sinusitis, tonsillitis, and pneumonia necessitated close monitoring. Studies in the rat model now indicate that experimental autoimmune MG can also be modulated by interfering with signaling between IFN-γ inducible protein 10 and its receptor CXCR3, suggesting this as a further potential treatment for MG.[2] Where all of this will lead remains to be determined but monoclonal antibodies appear to be a promising treatment worth future study. ■

References

1. Kakoulidou M, Pirskanen-Matell R, Lefvert AK. Treatment of a patient with myasthenia gravis using antibodies against CD25. *Acta Neurol Scand* 2008:117: 211-216.
2. Feferman T, Aricha R, Mizrachi K, et al. Suppression of experimental autoimmune myasthenia gravis by inhibiting the signaling between IFN-γ inducible protein 10 (IP-10) and its receptor CXCR3. *J Neuroimmunol* 2009;doi:10.1016/j.jneuroim.2009.01.021.

Risk of Shingles with Tumor Necrosis Factor Antibodies

ABSTRACT & COMMENTARY

By Joseph E. Safdieh, MD

Assistant Professor of Neurology, Weill Medical College, Cornell University

Dr. Safdieh reported that he received grant/research support from the American Academy of Neurology.

Synopsis: *When compared with conventional disease-modifying anti-rheumatic drugs (DMARD), tumor necrosis factor (TNF)-Alpha antibody treatment for rheumatoid arthritis (RA) may increase the risk of herpes zoster.*

Source: Strangfeld A, Listing J, Herzer P, et al. Risk of herpes zoster in patients with rheumatoid arthritis treated with anti-TNF-alpha agents. *JAMA* 2000;301:737-744.

EVER SINCE THEY WERE INITIALLY APPROVED BY THE U.S. Food and Drug Administration for the treatment of rheumatoid arthritis (RA), TNF-alpha receptor antibodies such as infliximab were known to induce an increased risk of bacterial infections, including tuberculosis. Much less is known about the risk of viral infections with these agents. Herpes zoster reactivation causes shingles and is more common in immune compromised patients, including those with HIV/AIDS and hematological malignancies and patients receiving chemotherapy. A causal relationship between TNF-alpha antibodies and varicella zoster virus (VZV) reactivation has never been clearly established. In this German prospective cohort study, the authors investigated whether TNF-alpha inhibitors, together as a class, or separately as either monoclonal anti-TNF-alpha antibodies (adalimumab, infliximab) or a fusion protein inhibitor (etanercept), are related to higher rates of herpes zoster in patients with RA.

The authors considered a patient as receiving anti-TNF-alpha treatment at the time of the herpes zoster infection if the treatment was ongoing or was terminated one month or less prior to the event. Incidence rates were calculated as the number of herpes zoster infections per 1,000 patient years of follow-up under specific treatment. A total of 5,040 patients were included in the analysis. Of note, patients receiving TNF-alpha agents were more likely to have worse disease severity and were more likely to be on oral corticosteroids.

The results demonstrated an incidence rate of 5.6 herpes zoster infections per 1,000 patient years in the control (DMARD) group compared to a 10.1 incidence rate in patients treated with anti TNF-alpha agents (8.9 for etanercept and 11.1 for infliximab/adalimumab). The hazard ratio for infliximab/adalimumab over DMARDs was 2.05, which reached statistical significance in univariate and multivariate analysis. Other factors which significantly increased the hazard ratio for the development of herpes zoster were advancing age (HR 1.28) and 10 mg or more of daily glucocorticoids (HR 2.52). Of note, very few patients developed post-herpetic neuralgia in any group and the rates of multidermatomal or ophthalmic zoster were increased in the TNF-alpha group, only, but the incidence rate was quite low at 2.5.

The authors conclude that treatment with monoclonal TNF-alpha antibodies may be associated with an

increased risk of herpes zoster, but caution that further study is needed.

■ COMMENTARY

The findings of this study should be of interest to neurologists. Of course, neurologists have experience with the development of viral infections caused by monoclonal antibodies from our experience with the development of progressive multifocal leukoencephalopathy associated with natalizumab treatment in multiple sclerosis trials. Interestingly, modulation of the TNF-alpha system may actually induce or worsen demyelinating disease in some reports, suggesting that it plays a role in central nervous system inflammation as well. Neurologists are all too familiar with shingles and its frequent consequence, post herpetic neuralgia (PHN). I found it interesting that in this study, only two patients developed PHN. Perhaps the immune suppression caused by the drugs that led to the development of shingles somehow protected against PHN, a phenomenon that has been described in the past, leading to the use of prednisone in shingles by some neurologists to prevent PHN. This study did not note the development of VZV vasculopathy or encephalitis in any patient. Generally, immune-compromised patients are at increased risk of developing encephalitis and small vessel vasculopathy, so the lack of development of these complications in the patients on TNF-alpha inhibitor therapy is interesting and perhaps somewhat surprising. ■

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 neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness. ■

CME Instructions

Physicians participate in this continuing medical education program by reading the articles, using the provided references for further research, and studying the CME questions. Participants should select what they believe to be the correct answers, then refer to the list of correct answers to test their knowledge. To clarify confusion surrounding any questions answered incorrectly, please consult the source material.

After completing this activity, participants must complete the evaluation form provided at the end of each semester (June and December) and return it in the reply envelope provided to receive a credit letter. When an evaluation form is received, a credit letter will be mailed to the participant.

In Future Issues: **Genetics and Stroke**

CME Questions

41. Deep brain stimulation for Parkinson's disease results in:
a. Reduction in dyskinesias
b. Reduction in tremor
c. Improved mobility and bradykinesia
d. Reduced levodopa dosage
e. All of the above

42. Autoantibodies that bind to beta amyloid deposits in the brain are:
a. decreased in Alzheimer patients.
b. inversely correlated to plaque burden in Alzheimer's patients.
c. only detectable after vaccination or passive immunization.
d. associated with increased microhemorrhage in Alzheimer's patients.

43. Poor prognostic signs for neurological recovery after cardiac arrest and resuscitation include all of the following EXCEPT:
a. Loss of background activity and reactivity on EEG
b. Loss of somatosensory evoked potential cortical response
c. Preservation of brain stem reflexes
d. Status epilepticus

44. Which of the following has NOT been shown to be a risk factor for craniocervical arterial dissection?
a. Ectomorphic body type
b. Endomorphic body type
c. Smoking
d. Migraine with aura
e. Connective tissue disorders

45. Potential treatments for autoimmune myasthenia gravis may include:
a. Rituximab
b. Basiliximab
c. Interfering with signaling between IFN-γ inducible protein 10 and its receptor
d. All the above
e. None of the above

46. TNF-alpha monoclonal antibody treatment for rheumatoid arthritis is associated with the following complications:
a. Bacterial infections
b. Tuberculosis
c. Herpes zoster
d. Demyelinating brain lesions
e. All of the above

Answers: 41. e; 42. b; 43. c; 44. b; 45. d; 46. e

Clinical Briefs in
Primary Care
The essential monthly primary care update
By Louis Kuritzky, MD
Supplement to *Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports.*
VOLUME 14, NUMBER 4 PAGES 7-8 APRIL 2009

VapoRub Revisited

Source: Abanses JC, et al. Vicks VapoRub induces mucin secretion, decreases ciliary beat frequency, and increases tracheal mucus transport in the ferret trachea. *Chest* 2009;135:143-148.

THOSE OF US IN THE BABY-BOOMER generation may recall in the 1940s-50s the application of a generous quantity of some Vicks® VapoRub-type salve (VvR) to the chest wall as a time-honored remedy that grandma suggested for the common cold. Toxicity of VvR, rather than efficacy, was the subject of this publication.

As with essentially any therapeutic agent, there is always the potential for adverse effects. Based upon a single case report of a toddler who developed respiratory distress subsequent to peri-nasal application of VvR, Abanses et al investigated potential adverse physiologic effects of VvR by experiments in ferrets.

VvR resulted in increased mucin secretion and decreased ciliary beat frequency (as observed by video microscopy), the combination of which could lead to small-airway obstruction. The authors report upon studies of menthol (an ingredient of VvR) in adults, in which, despite a decrease in nasal airflow, subjects universally report improved nasal symptoms; this change is attributed to the cooling effect of menthol in the nasal passages, which the brain interprets as increased airflow across the nostrils.

VvR appears to be a generally safe remedy, but case reports suggest caution in young children. The case presented here was initially treated as asthma; clinicians might consider asking about VvR use in children who present with new, otherwise unexplained symptoms of respiratory distress. ■

Prostate Cancer Risk with Testosterone Replacement

Source: Shabsigh R, et al. Testosterone therapy in hypogonadal men and potential prostate cancer risk: A systematic review. *Int J Impot Res* 2009;21:9-23.

GROWTH AND DEVELOPMENT OF THE prostate is recognized to be testosterone (TST)-dependent. Clinicians have long held concerns that TST therapy might not only worsen symptoms of benign prostatic hyperplasia (BPH), but also stimulate the development, growth, proliferation, or aggressiveness of prostate cancer (PCa). Some of this concern stems logically from the observation that TST deprivation has salutary effects on prostate cancer growth.

This systematic review of 44 articles using FDA-approved agents was unable to directly provide a definitive answer to the question of whether TST replacement increases risk of PCa, but provides other interesting insights. First, trials of hypogonadal men treated with TST have not evidenced an increased risk for PCa; if anything, a protective effect may occur. Second, TST-treated men with a history of PCa did not experience more recurrences or metastases. Third, TST did not appear to influence Gleason scores when PCa was detected.

The authors conclude, "There is no evidence that TST increases risk of prostate cancer in hypogonadal men." Of some concern, however, are the case reports of aggressive PCa in recipients of a non-FDA-approved supplement containing TST, estradiol, chrysin, and elk velvet antler. ■

The Suicidal Process: Time to Intervene?

Source: Deisenhammer EA, et al. The duration of the suicidal process. *J Clin Psychiatry* 2009;70:19-24.

SUICIDE HAS BEEN IN THE TOP CAUSES of death in the United States for more than 20 years, usually ranking among the top 10. Clinicians would like to play a useful role in suicide prevention, yet data are sparse to inform about the interval between first suicidal ideation and a suicide attempt. Deisenhammer et al attempted to bridge this knowledge gap with a study of persons with failed suicide attempts, all of whom (n = 82) were interviewed within 72 hours of attempted suicide.

Most (83%) subjects were alone at the time of suicide conceptualization, and almost half reported the time from first suicide conception to attempt was 10 min or less. Nonetheless, during this brief interval, most (77%) had some contact (usually by telephone) with friends or family, and the majority indicated their wish to die or (according to their subjective reports) hinted at their death wish.

Interviews with subjects did not provide any insight as to what might have deterred the suicide attempt. Nonetheless, the fact that most suicidal subjects did make contact with others leaves open the possibility that some component of interpersonal communication has the potential to change the course of suicide attempts. ■

BNP to Guide Treatment of Heart Failure

Source: Pfisterer M, et al. BNP-guided vs symptom-guided heart failure therapy. *JAMA* 2009;301:383-392.

For Americans aged 65 or older, congestive heart failure (CHF) remains the most common diagnosis for hospital admission. Despite advances in therapy, the outcome of CHF remains daunting, with 5-year mortality rates as high as many malignancies. Because brain natriuretic peptide (BNP) reflects left ventricular wall stress, it can be useful to assist in diagnosis of CHF. Additionally, some, but not all, clinical trials have suggested that intensification of therapy to achieve optimization of BNP is associated with improved outcomes. The Trial of Intensified vs Standard Medical Therapy in Elderly Patients with Congestive Heart Failure (TIME-CHF) was devised to provide a more definitive comparison between the success of treatment intensification based upon symptoms vs level of BNP.

Patients with CHF (n = 499) were randomized to BNP-directed management (titrate treatment until BNP < 400 ng/mL) vs symptomatic management (intensify treatment until NYHA class II symptoms or better). Follow-up for the primary endpoint—hospitalization-free survival—was 18 months.

The BNP group experienced more aldosterone antagonists use, as well as more frequent increases in dose and utilization of ACE inhibitors and ARBs. However, there was no difference in the primary endpoint. In subjects age < 75 years, there was a reduction in mortality favoring BNP-directed management; however, because this was a secondary endpoint and the primary endpoint did not achieve statistical significance, it must be considered exploratory, not established. BNP-guided intensification of treatment is no more effective than standard symptom-directed methods. ■

Clinical Briefs in Primary Care is published monthly by AHC Media LLC.

Associate Publisher: Coles McKagen. **Editor:** Stephen Brunton, MD. **Senior Managing Editor:** Paula Cousins. This is an educational publication designed to present scientific information and opinion to health professionals, stimulate thought, and further investigation. It does not provide advice regarding medical diagnosis or treatment for any individual case. It is not intended for the layman.

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Clopidogrel and CV Events: One Size Does NOT Fit All

Source: Simon T, et al. Genetic determinants of response to clopidogrel and cardiovascular events. *N Engl J Med* 2009;360:363-375.

Utilization of clopidogrel (CPG) in patients with acute coronary syndromes (ACS is well established. Similarly, long-term prophylaxis with CPG for secondary prevention of CV events is evidence-based: The CAPRIE trial indicated that CPG is marginally superior to aspirin for endpoint reduction, and the PROFESS trial demonstrated that ER-dipyridamole/aspirin (Aggrenox®) failed to meet the non-inferiority threshold when compared to CPG for stroke prevention.

Residual risk in persons receiving CPG remains substantial, suggesting that perhaps the efficacy of CPG is not universal; i.e., some subjects might metabolize CPG differently than others, leading to different levels of efficacy (or adverse effects).

The French Registry of Acute ST-Elevation and Non-ST-Elevation Myocardial Infarction (FAST-MI) study enrolled ACS patients on CPG, and studied the relationship of genetic variants that result in variations in absorption, activation, and biologic activity of CPG. Next, the relationship between these genetic variants and adverse outcomes (death, stroke, MI) were studied.

The most important genetic variant appeared to be at the P450 2C19 gene. Those with 2 loss-of-function 2C19 genes were almost 4 times as likely to have a CV event over the next year as those without. The P450 2C19 gene is utilized for metabolism of CPG to its active metabolite; lesser antiplatelet activity would be anticipated in persons with impaired P450 2C19 activity. These results support the findings of another trial in the same issue of *The New England Journal of Medicine* that identified increased CV risk in persons with reduced 2C19 P450 functionality. ■

Estrogen + Progesterone and Breast Cancer

Source: Chlebowski RT, et al. Breast cancer after use of estrogen plus progestin in postmenopausal women. *N Engl J Med* 2009;360:573-587.

The Women's Health Initiative (WHI) provided convincing evidence that the use of estrogen + progesterone (E+P) in postmenopausal women is associated with an increased risk of breast cancer (BrCa). The outcomes of this clinical trial motivated large numbers of women and their clinicians to rethink the risk-benefit balance of hormone therapy (HT), evoking a sea-change in prescribing habits.

Despite the acknowledged association between E+P and BrCa in WHI, a concomitant decline in use of mammography following the WHI news invited the possibility that post-WHI, less BrCa screening might have influenced the observed BrCa decline rather than simply less E+P use. To study this issue, WHI investigators evaluated two data sets: the original WHI population (n = 16,608 women without BrCa at baseline) and a second observational study population (n = 41,449 without BrCa at baseline). The observational study group did not receive advice about whether to use E+P, but were informed about the results of the interventional WHI when it became available. In the observational WHI population, more than 16,000 women were taking E+P at baseline.

Long-term follow-up of the observational WHI population showed an increased incidence of BrCa in women who had used E+P. BrCa incidence in this population declined subsequent to HT discontinuation. This suggests the possibility that some early breast cancers may regress or disappear if HT is stopped. The data did not, however, provide a meaningful association between lesser use of mammography and reduced BrCa. ■

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*.

Warfarin May Be First to Apply Pharmacogenetics

In this issue: Individualization of therapy with pharmacogenetics; the rate vs rhythm debate; the FDA's Risk Evaluation and Mitigation Strategy; FDA actions.

Individualization with pharmacogenetics

Get used to the word "pharmacogenetics" — the discipline of studying genetic variation and its effect on responses to drugs. Warfarin dosing may be one of the first clinical applications of pharmacogenetics as it now appears that genetic testing may help predict an individual patient's response to the oral anticoagulant. Warfarin dosing can vary as much as 10 times from individual to individual, and currently, slow titration with frequent testing is the only way to safely initiate therapy. A new study, however, uses pharmacogenetic testing to estimate the appropriate warfarin dose. Reviewing data from more than 4000 patients, algorithms were developed based on clinical variables only or clinical variables plus genetic information (CYP2C9 and VKORC1). Compared to algorithms employing clinical data alone, algorithms employing genetic information more accurately identified a larger proportion of patients who would require low-dose (49.4% vs 33.3%; $P < 0.001$) or high-dose warfarin (24.8% vs 7.2%; $P < 0.001$). The authors conclude that pharmacogenetic algorithms for estimating the appropriate initial dose of warfarin produces recommendations that are significantly closer to the required stable therapeutic dose than algorithms derived from clinical data alone or a fixed-dose approach, particularly for those that require 49 mg or more per week or 21 mg or less per week. (*N Engl J Med* 2009;360:753-764). Although pharmacogenetic testing is not yet widely available and may be difficult to obtain prior to initiating warfarin therapy, an accompanying editorial states "pharmacogenetics has the potential to increase benefit and reduce harm in people whose drug responses are not 'average.'" (*N Engl J Med* 2009;360:811-813).

The rate vs rhythm debate

Rate control vs rhythm control for atrial fibrillation continues to be debated with most of the evidence falling on the side of rate control in recent years, primarily because of adverse effects from anti-arrhythmics. A new drug may change that however. Dronedarone, a derivative of amiodarone, lowers the hospitalization rate and death rate in atrial fibrillation according to a new phase 3 study. More than 4600 patients with atrial fibrillation and one additional risk factor for death (diabetes, stroke, CHF) were randomized to dronedarone 4 mg twice a day or placebo. The primary outcome was first hospitalization due to cardiovascular event or death. After follow-up of 21 months, 30% of patients in the treatment group and 31% patients in the placebo group stopped the drug prematurely due to adverse events. The primary outcome occurred in 31.9% of patients in the dronedarone group vs 39.4% in the placebo group (hazard ratio, 0.76; 95% confidence interval,

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0.69-0.84; $P < 0.001$). Five percent (5%) of people died in the treatment group vs 6% in the placebo group ($P = 0.18$). Deaths from cardiovascular causes were 2.7% in the dronedarone group vs 3.9% in the placebo group ($P = 0.03$). The treatment group had higher rates of bradycardia, QT interval prolongation, nausea, diarrhea, rash, and increased creatinine levels. Dronedarone was not associated with higher rates of thyroid or pulmonary-related adverse events. The authors conclude that dronedarone reduced the risk of hospitalization due to cardiovascular events or death in patients with atrial fibrillation (*N Engl J Med* 2009;360:668-678). Dronedarone is not yet approved in this country, and is being evaluated for other cardiac arrhythmias as well as atrial fibrillation. A trial in heart failure (ANDROMEDA) was terminated early because of increased mortality associated with dronedarone (*N Engl J Med* 2008;358:2678-2687).

New rules for opioid prescribing

The FDA is considering new tightened restrictions on use of opioid drugs. Manufacturers of these drugs will be required to have a Risk Evaluation and Mitigation Strategy to ensure that "the benefits of the drugs continue to outweigh the risks." The affected opioids include fentanyl, hydromorphone, methadone, morphine, oxycodone, and oxymorphone. This is in response to raising rates of misuse and abuse of these drugs as well as accidental overdoses, which have increased in the last 10 years. The agency plans to have a number of meetings later this year that will include patient groups, federal agencies, and other non-government institutions. Part of the strategy is to make sure that physicians prescribing these products are properly trained in their safe use.

In February, the American Pain Society-American Academy of Pain Medicine Opioids Guidelines Panel published clinical guidelines for the use of chronic opioid therapy and chronic noncancer pain. The guideline was commissioned because of the increased use of chronic opioid therapy for noncancer pain and the high risk for potentially serious harm associated with these drugs including opioid-related adverse effects. The guideline's recommendations include: Before initiating chronic opioid therapy (COT), clinicians should conduct a history, physical, and appropriate testing including assessment of risk for substance abuse, misuse, or addiction. A benefit-to-harm evaluation should be performed and documented before starting COT and on an ongoing basis for all patients on COT. Informed consent should be obtained when initiating therapy, and a continuing discussion with the patient regarding therapy should include goals, expectations, risks, and alternatives. Clinicians may consider a written COT management plan. Patients should be reassessed periodically including monitoring of pain intensity and levels of functioning.

For high-risk patients or those who have engaged in aberrant drug-related behaviors, clinicians should periodically obtain urine drug screens or other information to confirm adherence to the plan of care. For patients at risk of addiction, mental health or addiction specialists should be consulted, and if aberrant drug-related behaviors continue, referral for assistance in management or discontinuation of COT should be considered. The guideline also deals with dose escalations, use of methadone, treatment of opioid-associated adverse effects, cognitive impairment associated with COT that may affect driving and workplace safety, use in pregnancy, and state and federal laws that govern the medical use of COT (*J Pain* 2009;10:113-130).

FDA Actions

The FDA has issued a public health advisory regarding the risk of progressive multifocal leukoencephalopathy (PML) associated with use of efalizumab (Raptiva®) for the treatment of psoriasis. Four cases have been reported (3 have been confirmed). The FDA is recommending that health care professionals monitor patients on efalizumab, as well as those who have discontinued the drug, for signs and symptoms of neurologic disease.

The FDA has reaffirmed its position regarding cholesterol-lowering drugs stating that "elevated amounts of low-density lipoprotein … are a risk factor for cardiovascular diseases … and that lowering LDL cholesterol reduces the risk of these diseases." The statement is in response to results from the ENHANCE trial, which indicated that there was no significant difference between simvastatin plus ezetimibe (Vytorin®) vs simvastatin alone (Zocor®) in reducing carotid atherosclerosis. There was, however, a greater reduction in LDL in the Vytorin group vs the Zocor group (56% reduction vs 39% reduction, respectively). The statement from the FDA suggests that the results of ENHANCE do not change the FDA's position that greater LDL lowering is beneficial, and recommends that patients currently on Vytorin or other cholesterol-lowering medications should not change their therapy. The update is available on the FDA's web site at www.FDA.gov. ■