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INSIDE

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Depression: A New Target for Deep Brain Stimulation?

ABSTRACT & COMMENTARY

By M. Flint Beal, MD

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

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

Synopsis: *Chronic stimulation of the white matter tracts adjacent to the subgenual cingulate gyrus was associated with a striking and sustained remission of depression in 4 of 6 patients.*

Source: Mayberg HS, et al. Deep Brain Stimulation for Treatment-Resistant Depression. *Neuron*. 2005;45:651-660.

MAJOR DEPRESSION IS A HUGE HEALTH PROBLEM, AND RANKS among the top causes of worldwide disease burden. It is the leading source of disability in adults in North America younger than age of 50. In many patients, depression is effectively treated with standard pharmacologic interventions, such as selective serotonin reuptake inhibitors. Some patients, however, require combinations of multiple medications and electroconvulsive therapy. Some of these patients still remain depressed despite these interventions. The present studies investigated whether deep brain stimulation in a specific cortical area, which has been linked to depression, would be effective in ameliorating the symptoms of depression. Depression has been linked to the limbic-cortical system network. Functional neuroimaging studies have shown that a critical role is played by the subgenual cingulate (CG25) in both acute sadness and anti-depressant treatment effects. This region may, therefore, play a critical role in mediating depression. A decrease in activity in this area has been reported with clinical response to a number of anti-depressant treatments, including selective serotonin reuptake inhibitors. There has also been a reduction in activity following electroconvulsive therapy. The critical region, CG25, has connections to the brain stem, hypothalamus, and insula, which have been implicated in disturbances of circadian rhythms associated with depression. These include disturbances of sleep, appetite, libido, and neuroendocrine changes. There are reciprocal pathways linking CG25 to orbital frontal, medial pre-

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frontal, and various portions of the anterior and posterior cingulate cortices. These are areas which have been strongly implicated in various aspects of learning, memory, motivation, and reward, which are strongly disturbed in depressed patients.

Deep brain stimulation has been shown to be effective in pathologically over reactive brain circuits. Mayberg and colleagues, therefore, tested whether deep brain stimulation in CG25 would reduce elevated activity and produce clinical benefits in 6 patients with refractory depression. Chronic stimulation of the white matter tracts adjacent to the subgenual cingulate gyrus was associated with a striking and sustained remission of depression in 4 of 6 patients. This was associated with a marked reduction in activity, as well as changes in downstream limbic and cortical areas, as assessed using positron emission tomography.

COMMENTARY

This study is the first to demonstrate that deep brain stimulation can be an effective treatment for refractory depression. Refractory depression can be totally disabling in some patients. Of note, however, only 4 of 6 patients showed a response. It is unclear why in the other 2 patients the treatment was ineffective. The procedure was well-tolerated. Deep brain stimulation may, therefore, become an effective and novel intervention treating patients who have disabling depression. ■

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

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Assistant Professor of the Department of Neurology at Weill Medical College, Cornell University

Dr. Henchcliffe is on the speaker's bureau for GlaxoSmithKline, Teva/Eisai, and Boehringer Ingelheim.

Synopsis: *Depression and anxiety in Parkinson's disease might be associated with a specific loss of dopamine and noradrenaline innervation in the limbic system.*

Source: Remy P, et al. Depression in Parkinson's Disease: Loss of Dopamine and Noradrenalin Innervation in the Limbic System. *Brain*. 2005;128:1314-1322.

THIS STUDY EXAMINED POSITRON EMISSION tomography (PET) images using [11C]RTI-32 as the tracer to study catecholaminergic neurotransmission in depression in Parkinson's disease (PD). [11C]RTI-32 binds with similar nanomolar affinities to the dopamine (DAT) and noradrenalin (NAT) membrane transporters. Patients fulfilling the diagnostic UK PDS Brain Bank criteria for idiopathic PD were divided in 2 groups, according to the presence (n = 8) or absence (n = 12) of major depression episodes defined by DSM-IV. Subjects had a mean age of 58.5 ± 7.9 years, disease duration of 0.5 to 9 years, and none had major depression prior to PD onset. All had a Mini-Mental Status score > 23 and were antidepressant-free for at least 3 months. The 2 groups were well matched for age, disease duration and severity, and antiparkinsonian medications. Neuropsychiatric evaluation included the Beck Depression Inventory (BDI), the Apathy Evaluation Scale (AES), and the State Trait Anxiety Inventory (STAI) for quantification of depression, apathy, and anxiety. PET and MRI images were acquired with subjects off PD medication. Images were analyzed by regions of interest (ROI) and voxel-based statistical parametric mapping (SPM99). Depressed PD patients had higher mean scores than the non-depressed patients on BDI (19.1 ± 7.0 vs 5.5 ± 2.5points), AES (18.8 ± 7.3 vs 5.2 ± 2.7), and STAI (50.3 ± 16.6 vs 32.3 ± 8.7) scales. Tracer uptake, analyzed by ROI, was higher in non-depressed compared to depressed PD patients, in the thalamus, locus coeruleus,

amygdala, and anterior cingulate cortex. SPM99 analysis revealed higher tracer binding for non-depressed over depressed PD patients in the locus coeruleus bilaterally, the mediodorsal and inferior thalamus bilaterally, the left ventral striatum, and the right amygdala. Moreover, there was an inverse correlation of BDI score with tracer binding in the left ventral striatum of AES score, with tracer binding to ventral striatum bilaterally, and of STAI score with left ventral striatum, left caudate, left locus coeruleus, left inferior thalamic region, and bilateral amygdala and medial thalamus tracer binding.

COMMENTARY

Depression prevalence rates reported vary widely between 20 to 45% in PD,[1] and its diagnosis in PD patients is confounded by non-motor phenomena, such as psychomotor slowing, apathy, and abulia, overlapping with depressive symptoms. The present study exploits functional neuroimaging to obtain insight into the pathophysiology of this often difficult to treat, comorbid condition in PD. It demonstrates reduced binding of [11C]RTI-32 to crucial regions of the limbic system in depressed compared to non-depressed PD subjects. Since [11C]RTI-32 binds both DAT and NAT, interpretation of binding changes depends on knowledge of the distribution of these transporters. Remy and colleagues suggest that changes in the locus coeruleus and thalamus, as well as amygdala and ventral striatum (to which the locus coeruleus sends noradrenergic projections), are due at least in part to changes in noradrenergic neurotransmission. Despite limitations, clinical implications for PD depression are interesting. Many depressed PD patients are treated with serotonin re-uptake inhibitors (SSRI), which have little direct effect upon the noradrenergic system, and strong evidence supporting their efficacy is lacking. Nortriptyline, affecting both noradrenergic and serotonergic systems, has been shown in a small trial to be effective in treating depressed PD patients. Unfortunately, its use is hampered by anticholinergic and sedating side effects. Based on results of this article, serotonin-noradrenalin re-uptake inhibitors (SNRI), such as venlafaxine, may prove to be more effective than SSRIs for relief of PD depression, and this is under examination by the NIH-sponsored phase III Study of Anti-depressants for Parkinson's Disease (SAD-PD) comparing paroxetine vs venlafaxine.[2]

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Long-Term Follow-Up of Deep Brain Stimulation in Parkinson's Disease

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD

Synopsis: *Deep brain stimulation (DBS) is associated with significant improvement of motor complications in patients with severe Parkinson's disease after some 6-12 months of treatment.*

Source: Rodriguez-Oroz MC, et al. Bilateral Deep Brain Stimulation in Parkinson's Disease: A Multicentre Study With 4 Years Follow-Up. *Brain*. June 23, 2005; (Epub ahead of print).

RODRIGUEZ AND COLLEAGUES PROSPECTIVELY STUDIED 69 patients with advanced Parkinson's disease (PD) over a 3- to 4-year period, after bilateral deep brain stimulation (DBS) at 8 centers in Europe and Canada. Stimulation site depended on investigator judgment, rather than randomization, with the subthalamic nucleus (STN) targeted in 49 subjects and the globus pallidus internus (GPi) in 20. Mean age in the STN group was similar (STN: 59.8; range, 38-75 years; GPi: 55.8; range, 43-70 years), and mean disease duration was 15.4 years in each group. Baseline motor scores on the Unified Parkinson's Disease Rating Scale (UPDRS) Part III motor subscale were similar, but baseline scores for dyskinesias on medication were higher in the GPi group (2.83 ± 1.18 on a UPDRS subscale 1-4) than the STN group (1.95 ± 1.07). The STN group took more levodopa equivalents (1336 ± 619 mg/day) than the GPi group (1074 ± 462 mg/day) prior to surgery. Primary outcome measure was change in UPDRS motor subscale off medication, on stimulation at 3 to 4 years postoperatively, compared to baseline. Both groups maintained substantial improvements (STN: 56.7 ± 15.7 to 28.6 ± 15.7, $P < 0.001$; GPi: 51.7 ± 13.6 to 31.7 ± 12.8, $P < 0.001$). However, gait, postural stability, and speech subscales significantly declined at 3 to 4 years in the STN group, despite improvement at 1 year. In contrast,

changes in the GPi group were not statistically significant. Dyskinesias on medication improved in both groups (STN: 1.95 ± 1.07 to 0.80 ± 0.78; GPi: 2.83 ± 1.18 to 0.68 ± 0.75). Levodopa equivalent intake was reduced from mean 1309 ± 649 to 859 ± 659 mg/day in the STN group at one year, with no further significant change at the end of the study. However, GPi patients' daily levodopa equivalents did not significantly change. Persistent adverse effects were reported in 53% and 35% of the STN and GPi groups, respectively. Twelve STN patients suffered cognitive decline (8 rated moderate-severe), compared to 1 GPi patient (mild), and 3 STN patients had mood disturbances not reported in GPi patients. Nine STN patients suffered dysphonia or dysarthria, compared to 1 GPi patient. Six from the STN group and 1 from the GPi group required repeat surgery for lead fracture, skin erosion, or infection, and 2 patients discontinued DBS therapy due to infection.

COMMENTARY

This important article demonstrates maintenance of benefit for DBS of both STN and GPi targets at 3 to 4 years post-procedure in the UPDRS motor subscale for a highly selected group of PD patients with advanced disease. Off periods and dyskinesias were dramatically reduced, as in previous short-term studies. Krack and colleagues recently published their experience with STN stimulation at 5 years follow up.[1] They similarly demonstrated that, despite maintenance of benefit for classic levodopa-responsive features of PD, speech deficits and postural instability gradually accrued in patients treated with STN DBS. In the present study, Rodriguez-Oroz and colleagues found that GPi-stimulated patients fared better for speech, postural stability, and gait, and additionally had a better adverse event profile than STN patients. Unfortunately, with lack of randomization, it is likely that particular subpopulations of PD patients were selected for the 2 target sites. Moreover, GPi patients required more levodopa after surgery (possibly as dyskinesias ameliorated, allowing correction of prior under-medication): therefore, off scores at 12 hours after medication withdrawal could appear better because of long-term medication effects. Although not designed as a head-to-head comparison of STN and GPi as targets for DBS, these findings clearly require further study to clarify their potential clinical significance regarding target choice in individual PD patients. Finally, despite careful patient screening, significant cognitive decline and mood disturbances were noted in a subset of patients. These non-motor symptoms are common in elderly patients, and it is imperative we better understand their relationship to DBS.

References

1. Krack P, et al. Five-Year Follow-Up of Bilateral Stimulation of the Subthalamic Nucleus in Advanced Parkinson's Disease. *N Engl J Med*. 2003;349: 1925-1934.
2. Oxman MN, et al. A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults. *N Eng J Med*. 2005;352:2271-2284.

A Vaccine to Prevent Shingles—Treating Post-Herpetic Neuralgia in a Pre-Herpetic State

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD

Assistant Professor, Department of Neurology, Weill Cornell Medical College, and Attending Neurologist at NewYork-Presbyterian Hospital

Dr. Segal is on the speaker's bureau of Boehringer-Ingelheim.

Synopsis: *There was an increased incidence of injection site reactions among vaccine treated patients, but no difference in the incidence of serious adverse events.*

Source: Oxman MN, et al. A Vaccine to Prevent Herpes Zoster and Postherpetic Neuralgia in Older Adults. *N Eng J Med*. 2005;352:2271-2284.

Herpes zoster, or shingles, occurs due to reactivation of Varicella-Zoster Virus (VZV) infection, which lies dormant in both cranial nerve and dorsal root ganglia. Shingles itself may be an annoyance, but the syndrome of post-herpetic neuralgia (PHN) is a source of severe and potentially debilitating chronic pain. Current treatment options, either topical (eg, lidocaine patches or capsaicin cream) or oral (eg, gabapentin, carbamazepine, or amitriptyline), are suboptimal. Shingles can occur at any age, but are more common in the elderly who tolerate medications poorly and are more likely than the young to develop PHN. VZV immunity, produced by infection as a child, wanes over time as cell-mediated immune responses become gradually less robust with age. Soon to

enter middle age will be a population of patients who received a now available VZV-vaccine as a child. These individuals may have a lower shingles risk due to a lower latent viral ganglionic burden than those who had chicken pox as children. Alternatively, the childhood vaccine may produce an initially less robust immune response that would be even more prone to attrition over time, compared with that from natural disease. The study by Oxman and colleagues suggests that a booster zoster vaccine, given to healthy elderly volunteers, could effectively prevent shingles and significantly reduce post-herpetic pain complications.

Oxman et al's study utilized the Oka/Merck VZV vaccine. This investigational agent contains approximately 18,700 to 60,000 plaque-forming units of live-attenuated virus. This is in contrast to the currently approved pediatric vaccine, which contains a lower inoculum of approximately 1350 units. The study included over 38,000 patients, aged greater than 60, who were randomized in double blind, randomized, placebo-controlled manner, and were followed for 3 years. There were 315 cases of shingles confirmed in vaccine treated patients, compared to 642 in the placebo group. Of note, the placebo incidence of shingles was approximately 1/100 person-years, exactly in keeping with known epidemiological data. There were 107 cases of post-herpetic neuralgia (27 in vaccine treated patients and 80 among placebo). This 66.5% reduction in post-herpetic neuralgia was highly statistically significant ($P < 0.001$). Overall efficacy was calculated according to a burden of illness score, which was 61.1% lower in vaccine treated patients ($P < 0.001$). There was an increased incidence of injection site reactions among vaccine treated patients, but no difference in the incidence of serious adverse events.

COMMENTARY

Given the challenges that face neurologists in finding effective therapies for their patients with PHN, the potential to prevent this disease should come as welcome news. The high dose VZV vaccine used by Oxman et al is not yet available, and as Oxman et al note, it cannot be expected that their results could be replicated with the substitution of the low dose currently FDA-approved alternative. Widespread use of a VZV vaccine among the elderly would come at some expense, but it is likely that this would be outweighed by both the calculable costs of PHN treatments and the incalculable quality of life benefits that PHN prevention would bring. ■

Idiopathic Polyneuropathy

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology at NewYork-Presbyterian Hospital, Cornell Campus

Dr. Rubin is on the speaker's bureau for Athena Diagnostics and does research for Pfizer and Merck.

Synopsis: *Patients presenting with symptoms of polyneuropathy but who have neither neurological signs of polyneuropathy nor electrophysiological studies confirming a polyneuropathy have a good outcome at least 2 years after presentation.*

Source: Rosenberg NR, et al. Follow Up of Patients With Signs and Symptoms of Polyneuropathy Not Confirmed By Electrophysiological Studies. *J Neurol Neurosurg Psychiatry.* 2005:76:879-881.

PATIENTS WITH SYMPTOMS AND SIGNS OF polyneuropathy, yet with normal electrophysiological studies, are a common conundrum in clinical practice. What can we counsel these patients regarding prognosis? Retrospective review of all such patients seen between 1993-1998 in an outpatient department of a university medical center was undertaken to address this question. All patients were symptomatic, complaining of tingling, burning, pain, numbness, muscle weakness, cramps, or stiffness, and had signs consistent with polyneuropathy, including impaired vibratory, pin-prick, temperature, joint-position, light touch sensation, hyperpathia, muscle weakness, wasting, fasciculations, and loss of deep tendon reflexes. Patients over 65 years were considered normal despite absence of ankle reflexes, atrophy of the extensor digitorum brevis muscle, or impaired vibration sensation at the big toe. All patients had undergone nerve conduction studies, including thermo-sensory threshold testing if a small fiber neuropathy was suspect. Follow-up, performed at 2 years, consisted of the physical section of the Sickness Impact Profile (SIP) categorized as a good (minor symp-

toms, score < 75 percentile) or poor outcome (severely disabled, score > 75 percentile).

Among 489 persons referred for possible polyneuropathy between 1993-1998, 397 underwent electrodiagnostic studies, 139 of which did not demonstrate evidence of neuropathy. Of these, clinical criteria for neuropathy were not fulfilled in 27 who were excluded, and an additional 38 were not available for follow-up at 2 years, leaving 74 subjects eligible for this study, 35 with symptoms only, and 39 with both symptoms and signs.

Among 15 women and 20 men with symptoms only, mean age was 51 years. Three yielded a diagnosis by follow-up, one each with conversion, erythromelalgia, and ciguatera intoxication. Only one patient among the 35 suffered a poor outcome due to unrelated multiple embolic infarcts. Among 19 women and 20 men with both symptoms and signs, mean age was 58 years, and 24 yielded diagnoses, including spinal stenosis (n = 9), multiple sclerosis (n = 5), dural arteriovenous fistula (n = 2), and 1 each with meningioma, intramedullary tumor, plexopathy, radiculopathy, intermittent claudication, spinal muscular atrophy, syringomyelia, and B12 deficiency. Fifteen of 74 patients were found to have risk factors for polyneuropathy, encompassing diabetes or alcohol abuse, or both, and renal disease.

Diagnosis in idiopathic chronic polyneuropathy is possible in over 60% of patients with both symptoms and signs, even in the absence of electrodiagnostic confirmation, but in less than 10% with symptoms only. Patients in the latter group may be reassured that prognosis is excellent.

COMMENTARY

Do statins (HMG-CoA-reductase inhibitors) cause idiopathic polyneuropathy (IPN)? No, it appears they do not. From a database of 915,066 patients, encompassing 23 affiliated hospitals in Utah and neighboring states, 272 patients were identified as having been admitted with a diagnosis of IPN over a 4-year period. None carried a diagnosis of diabetes, renal insufficiency, alcoholism, cancer, AIDS, Lyme disease, heavy metal intoxication, or hypothyroidism. Neither dosage nor duration of statin use prior to the diagnosis was found to be significantly different in IPN patients, compared to 1360 matched controls.

The Treatment of TIAs: The Long and Short of It

ABSTRACTS & COMMENTARY

By John J. Caronna, MD

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

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

Synopsis: *Acute MRI is useful in making triage decisions for patients with TIA or minor stroke because it reliably divides such patients into benign, intermediate, and poor prognosis groups.*

Sources: van Wijk I, et al. Long-Term Survival and Vascular Event Risk After Transient Ischaemic Attack or Minor Ischaemic Stroke: A Cohort Study. *Lancet*. 2005;365:2098-2104; Hankey GJ. Redefining Risks After TIA and Minor Ischaemic Stroke. *Lancet*. 2005;365:2065-2066; Coutts SB, et al. Triaging Transient Ischaemic Attack and Minor Stroke Patients Using Acute Magnetic Resonance Imaging. *Ann Neurol*. 2005;57:848-854.

The short-term prognosis and risk factors for stroke after TIA have been well studied (Johnston SC, et al. *JAMA* 2000; 284: 2901-2906). In most clinical studies reported so far, however, the follow-up of patients with TIA or stroke has lasted no more than 3 to 5 years. Therefore, Van Wijk and colleagues sought to study determinants of survival and the occurrence of vascular events in the long term after a TIA or minor or ischemic stroke. They prospectively followed more than 2400 patients who had had a TIA or minor stroke and had been enrolled in the Dutch TIA Trial between 1986 and 1989. (The Dutch TIA Trial Study Group. *N Engl J Med*. 1991;325:1261-1266).

Follow-up was complete in 2447 patients (99%). After a mean follow-up of 10 years, 1489 patients (60%) had died. Of these, three quarters were vascular deaths (ischemic stroke, cerebral hemorrhage, myocardial infarction, congestive heart failure, sudden death, or other vascular cause). The cumulative risk of death was approximately 3% at one year, 19% at 5 years, and 43% at 10 years after enrollment.

The strongest predictors of death from any cause were age over 65 years (Risk Ratio {RR} 3.33), diabetes (RR 2.10), previous peripheral vascular surgery (RR 1.94), history of claudication (RR 1.77), and pathological Q-waves or negative T-waves on baseline electrocardiogram (RR 1.59). Angina pectoris was not a predictor of death (RR 1.3).

During the period of follow-up, 1366 patients (54%) had at least one vascular event. The 10-year risk of vascular events for patients with TIA was 36%, and for those with minor stroke, it was 48%. Cumulative risk of a major vascular event was 7% at one year, 24% at 5 years, and 44% at 10 years. The mean yearly recurrence rate was 6%; it gradually declined during the first 3 years from 7% to 3.5%, but steadily increased over time thereafter. The strongest predictors of a vascular event were identical to the strongest predictors of death.

Coutts and colleagues prospectively examined the predictive value in the short term (90 days) of acute MRI scanning and MR angiography in patients presenting with an acute TIA or minor stroke. One hundred twenty TIA or minor ischemic stroke patients (NIH Stroke scale score < 3) presenting to a single academic institution in Canada were examined by a stroke neurologist within 12 hours of onset and had brain MRI scanning and MR angiography performed with 24 hours.

The 90-day risk for stroke in this cohort was 12%, and the high risk period was within the first 48 hours of the initial event. Sixty-four percent of events occurred within this period. Patients with a diffusion weighted imaging (DWI) lesion were at greater risk for stroke than patients without a lesion, and the risk was greatest in those with both a DWI lesion and an intracranial vessel occlusion. The 90-day risk rate for patients with no DWI lesion was 4%; for those with a DWI lesion but no vessel occlusion, the risk rate was 11%; and for those with a DWI lesion and a vascular occlusion, the risk rate was 33% ($P = 0.02$). At 3-month follow-up, a high proportion of these patients (21%) were dependent vs 2% of patients with no DWI lesion and 6% of patients with only a DWI lesion. Coutts et al conclude that acute MRI is useful in making triage decisions for patients with TIA or minor stroke because it reliably divides such patients into benign, intermediate, and poor prognosis groups.

COMMENTARY

Van Wijk et al confirmed that the risk of stroke and other major vascular events remains high over the 10 years after TIA or minor ischemic stroke. Interestingly, the annual risk for recurrent vascular events was not linear: it was high early, declined to a low point at 3 years, and then progressively increased. This late increase probably reflects continued exposure to vascular disease-inducing risk factors, an increase in atherosclerotic plaque burden, and increasing age. In this particular cohort, however, it could reflect a decline in drug compliance after the end of the Dutch TIA Trial and reduced attention to lifestyle factors. If so, risk-factor modification and drug therapy may improve the long-term secondary prevention of vascular events.

The study of Coutts et al underlines the utility of the tools now available to aid in the emergent diagnostic evaluation of patients with cerebrovascular disease. DWI and perfusion MRI performed early can help the clinician to select patients who might benefit from reperfusion and neuroprotectant agents. Nevertheless, as pointed out by Hanley in his comments, the report of Van Wijk showed the predictive power of history taking alone. Simply by asking the patient about age, history of myocardial infarction, diabetes, hypertension, and peripheral vascular disease, the clinician can obtain almost as much information about risk of a future vascular event as from the neurological examination and diagnostic procedures. ■

High-Dose Methylprednisolone for Acute Spinal Cord Injury—Do Serious Side-Effects Outweigh Potential Benefit?

ABSTRACT & COMMENTARY

By Matthew Fink, MD

Vice Chairman, Professor of Clinical Neurology, Weill Medical College, and Chief of Division of Stroke and Critical Care Neurology at NewYork-Presbyterian Hospital

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

Synopsis: *High-dose methylprednisolone (MP) appears to cause severe acute corticosteroid myopathy (ACM) in patients with acute traumatic spinal cord injury (ASCI), and along with other steroid-related complications, casts doubt on the benefit of MP treatment for ASCI.*

Source: Qian T, et al. High-Dose Methylprednisolone May Cause Myopathy in Acute Spinal Cord Injury Patients. *Spinal Cord*. 2005;43:199-203.

THE USE OF HIGH-DOSE METHYLPREDNISOLONE (MP) for treatment of acute traumatic spinal cord injury (ASCI) has been used worldwide since the publication of the National Acute Spinal Cord Injury Studies (Bracken, et al. *N Engl J Med*. 1990;322:1405-1411 and Bracken, et al. *J Neurosurg*. 1992;76:23-31). The protocol recommends the highest dosage of any corticosteroid used during a 24-hour period for any reported

clinical condition (MP 30 mg/kg IV in the first hour and maintained on 5.4 mg/kg/hr for the next 23 hours). Since the publication of the NASCIS, no other group has replicated the results, and several have pointed out the increased risk of steroid-induced complications, including hyperglycemia, sepsis and pneumonia.

Qian and colleagues diagnosed acute corticosteroid myopathy (ACM) in 5 consecutive patients treated with the NASCIS protocol. Muscle biopsy performed 3 to 7 days after MP treatment demonstrated acute myofiber necrosis and severe type II muscle atrophy in 4 of 5 patients. The fifth patient had a normal biopsy, but this was performed within the first 24 hours, before one would expect to see pathologic changes. All 5 patients had EMG findings consistent with myopathy-positive sharp waves and fibrillations in all muscles tested 2 to 4 weeks after injury. Three additional patients with ASCI who were not treated with corticosteroids underwent the same studies, muscle biopsy, and EMGs, and were found to be completely normal.

COMMENTARY

Since the publication of the NASCIS, many investigators have questioned the validity of the study conclusion, that high-dose MP treatment is better than placebo in patients with ASCI. In a detailed meta-analysis of the literature that reviewed all available studies to date, Short, et al. (*Spinal Cord*. 2000;38:273-286) was unable to find any study that replicated the results of the NASCIS. They also pointed out that the only significant findings came from a post-hoc, sub-group analysis of patients treated within 8 hours of injury, and that the group had improvement in sensory symptoms only. At one year follow-up, the NASCIS investigators stated "considering all randomized patients at 1 year, there were no significant differences in the neurological function by the treatment group." The MP group showed a slight advantage (sensory examination) over placebo, but one must decide if this translates into clinical significance, as well as statistical significance.

Qian, et al have now demonstrated that high-dose MP causes severe ACM. This syndrome has been well documented in a variety of clinical conditions, particularly in acute asthma and in other critically ill patients who undergo paralysis with neuromuscular blocking agents. In patients with ASCI, the development of ACM from high-dose MP may explain the difference in clinical course between steroid-treated and placebo-treated patients from the NASCIS. The investigators may have observed the recovery from ACM, rather than from ASCI.

In addition to other steroid complications, ACM may cause respiratory impairment by causing myofiber necrosis of diaphragmatic muscle, resulting in prolonged mechanical ventilation. Along with hyperglycemia, sepsis, and pneumonia, ACM makes the use of high-dose MP hazardous in patients with ASCI. The NASCIS protocol for ASCI is not supported by current standards of evidence-based medicine and should not be considered a standard of care. Additional neuroprotective strategies should be developed for the treatment of ASCI using placebo controls.

CME Questions

3. Idiopathic chronic polyneuropathy:
   a. statins may be causative.
   b. underlying diagnosis is possible in over 50% with symptoms only.
   c. patients, with symptoms only, may be reassured that prognosis is excellent.
   d. is a rare condition.
   e. None of the above is true

4. After a TIA or minor ischemic stroke, the risk of another vascular event:
   a. progressively declines over 10 years.
   b. progressively declines after 3 years.
   c. progressively increases after one year.
   d. progressively increases after 10 years.
   e. initially decreases over 3 years then progressively increases.

Answers: 3. (c); 4. (e)

CME Objectives

The objectives of *Neurology Alert* are:

•To present current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

•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; and

•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.

In Future Issues:

Fatigue in MS