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INSIDE

Therapeutic Vaccine for ALS?

ABSTRACT & COMMENTARY

Source: Angelov DN, et al. Therapeutic vaccine for acute and chronic motor neuron diseases: Implications for amyotrophic lateral sclerosis. *Proc Natl Acad Sci USA*. 2003;100:4790-4795.

THIS ARTICLE REPORTS THE NOVEL OBSERVATION THAT THERAPEUTIC vaccination with Copaxone (glatiramer acetate, Cop-1), protects motor neurons against acute and chronic neurodegenerative conditions. Angelov and colleagues examined acute degeneration after facial nerve axotomy. They found that the number of surviving motor neurons was 2-fold greater in Cop-1 vaccinated mice as compared to nonvaccinated mice. Furthermore, they found that administration of Cop-1 to transgenic mice with the G93A mutation in copper zinc superoxide dismutase significantly improves life span as compared to unmatched controls. They found an increase in life span of approximately 25% in low-expressing mice. There was also a delay in the disease onset as assessed by motor performance. An increase in life span and a high-expressing G93A SOD1 mouse line, however, did not exceed 10%. Angelov et al conclude that they have induced protective autoimmunity and that Cop-1 vaccination boosts the local immune response needed to combat destructive self-compounds associated with motor neuron death.

COMMENTARY

These results are unprecedented and certainly of interest. Angelov et al have a long-standing interest in the possibility that the initial immune response may be neuroprotective rather than neurodestructive. They have examined a number of other models previously with vaccination and have demonstrated that preimmunization prior to insults, such as mechanical crush injury or axotomy or biochemical insults with glutamate or oxidative stress, results in a neuroprotective response. They, therefore, hypothesized that the protective T-cell mediated response might be boosted without risk of an autoimmune disease induction by administrating Copolymer-1 (Copaxone), a synthetic polypeptide consisting of the amino acids tyrosine, glutamate, alanine, and lysine. This compound is presently in clinical use for multiple sclerosis. It has been shown to activate a wide range of self-reactive T cells. In a model of a chronic neurodegenerative disorder associated with optic nerve neu-

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ropathy induced by experimental glaucoma, Cop-1 vaccination significantly increased neuronal survival. The present results demonstrating that vaccination produced protection against motor neuron degeneration induced by acute facial nerve axotomy are of considerable interest. Angelov et al also found that immunization of Cop-1 at the age of 60 days into low-expressing transgenic mouse models of ALS significantly improved survival by 25%. This is a relatively good increase. However, a caveat is that this was in the low-expressing mice, which show a bigger response to a variety of therapies than the high-expressing mice. The improvement in the high-expressing mice was not impressive. Angelov et al also demonstrated that administration of Cop-1 significantly delayed the onset of impaired motor performance. The present results, therefore, suggest that Cop-1 might be a useful treatment for ALS. This is consistent with other evidence that certain immune modulators exert protective effects in transgenic mouse models of ALS. For instance, minocycline has been shown to delay the progression of symptoms in a mouse model of ALS in 3 different studies. This drug has anti-inflammatory activities, which may be related to its beneficial effects, and has now entered clinical trials. The present results are of considerable interest but need further experimental studies before they can be applied to humans.

— M. FLINT BEAL

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Pallidotomy vs Medical Therapy for Parkinson's Disease

ABSTRACT & COMMENTARY

Source: Vitek JL, et al. Randomized trial of pallidotomy versus medical therapy for Parkinson's disease. *Ann Neurol*. 2003;53:558-569.

SURGICAL TREATMENT FOR PARKINSON'S DISEASE has become increasingly used as a modality of treatment. Nevertheless, the efficacy and its long-term outcomes as compared to medical therapy are not well established. In the present report, 36 patients with Parkinson's disease were randomized to either medical therapy (n = 18) or unilateral GPi pallidotomy (n = 18). Vitek and associates followed as a primary outcome variable the change in the total Unified Parkinson's Disease Rating Scale (UPDRS) score at 6 months of follow-up. At 6 months, the patients receiving pallidotomy had a statistically significant reduction of 32% in the total UPDRS score, as compared to those on medical therapy who showed a 5% increase. The patients who received surgery showed improvement in all the cardinal motor signs of Parkinson's disease including tremor, rigidity, bradykinesia, gait, and balance. Drug-induced dyskinesias were also markedly improved. The improvement was greatest on the side contralateral to the lesion; however, there was also a significant improvement ipsilateral to the lesion for bradykinesia, rigidity, and drug-induced dyskinesias. A total of 20 patients have been followed for 2 years to assess the long-term effects on clinical outcome. These patients have shown sustained improvement on the UPDRS "off" motor scale, as well as complications of therapy subscores. Sustained improvement was only seen for tremor, rigidity, bradykinesia, percent on time, and drug-induced dyskinesias.

COMMENTARY

As discussed in prior issues, there are a number of advances, which are taking place for the treatment of Parkinson's disease. These include neuroprotective strategies, neurorestoration strategies with GDNF, as well as neuroreplacement with stem cells. The fourth advance in treatment, which has become highly used over the past several years, is surgical treatment. The major modalities, which have been studied, are lesions in the globus pallidus interna (Gpi) and deep-brain stimulation in the subthalamic nucleus. The present report is one of the best controlled and evaluated studies of the effects of GPi pallidotomy in

PD patients. Vitek et al have clearly documented improvement at 6 months as compared to medical therapy and demonstrated that the benefits were sustained for 2 years of follow-up. A previous trial in a multicenter study did not report follow-up longer than 6 months. An earlier study without microelectrode recording reported results similar to those in the present results at 6-12 months of follow-up, but by 2 years the patients had largely returned to baseline levels of functioning. Vitek et al, therefore, feel that using microelectrodes to localize lesions is very important in obtaining successful long-term improvement. A number of other groups found sustained long-term benefit with unilateral pallidotomy. A few of the prior studies showed effects only on certain symptoms in Parkinson's patients. For instance, one showed an effect on bradykinesia but only a moderate effect on tremor, and another reported little effect on tremor but a significant effect on rigidity. Others reported improvement of both tremor and bradykinesia. The present report showed improvement in all clinical variables. Particularly notable was improvement in balance, which is usually resistant to drug therapies. Vitek et al observed improvement in dyskinesias. This has been one of the most consistent outcomes with pallidotomy in the GPi. Vitek et al note that the lesions, which are effective, may be localized to different parts of the GPi. It is known that the circuitry into these different portions differs. It was reported that tremor was alleviated to a significantly greater degree, with lesions placed more posteriorly in the GPi whereas rigidity was alleviated with more anteriorly placed lesions. Vitek et al note that it is important to avoid lesioning the GPe. The one patient in the present cohort who did not improve after pallidotomy had a lesion that involved a large portion of the posterior portion of GPe. Similarly, in another study in which pallidotomy was reported to have little benefit, the reported lesion size was considerably larger, and there may have been partial involvement of GPe. Another factor, which they evaluated, was the age of the patients in response to outcome from pallidotomy. Vitek et al observed that there was a clear and significant relationship of age to clinical outcome with younger patients showing significantly more improvement than older patients independent of disease duration. This is consistent with a prior report from Lang and associates, who reported greater improvement for patients younger than 65 vs those older than 65.[1]

Overall, this study provides clear evidence that pallidotomy is an effective treatment for the motor symptoms associated with advanced Parkinson's disease, and can provide lasting benefits on both ipsilateral as well as contralateral rigidity, bradykinesia, and drug-induced dyskinesia. These data provide further evidence that this is a useful treatment modality for advanced Parkinson's disease. — **M. FLINT BEAL**

Reference

1. Lang AE, et al. *N Engl J Med*. 1997;337:1036-1042.

Machado-Joseph, Muscle Cramps, and Mexiletine

ABSTRACT & COMMENTARY

Source: Kanai K, et al. Muscle cramp in Machado-Joseph disease: Altered motor axonal excitability properties and mexiletine treatment. *Brain*. 2003;126:965-973.

Spinocerebellar ataxia type 3, Machado-Joseph disease (MJD), is an adult onset, autosomal-dominant disorder often presenting as a combination of upper and lower motor neuron signs, including facial and tongue fasciculations, resembling amyotrophic lateral sclerosis (ALS). Associated findings include extrapyramidal signs (dystonia, rigidity), progressive external ophthalmoplegia, and peripheral neuropathy. MJD is the result of a CAG triplicate repeat expansion on chromosome 14q32.1.

In an attempt to shed light on the incidence and pathophysiology of muscle cramps, their clinical and electrical characteristics were studied in 20 genetically confirmed MJD patients. Comparison was made to patients with ALS (n = 22), chronic axonal peripheral neuropathy (PN; n = 37), spinal muscular atrophy (SMA; n = 6), and to 32 age-matched normal controls. Measurements of motor axon excitability included strength-duration time constant (reflective of Na+ channel function), threshold electrotonus (reflective of K+ channel function), refractoriness, and supernormality. Statistical analysis was performed using the Mann-Whitney U test, the paired t-test, and Spearman's rank correlation.

Sixteen MJD patients (80%) experienced frequent and severe muscle cramps affecting muscles of the limbs and trunk, a frequency greater than that for PN (24%) or SMA (33%) but not unlike that seen in ALS (68%). MJD patients demonstrated a significantly longer strength duration time constant compared to normals (P = .001), as did the PN and SMA groups. ALS and normals did not significantly differ in strength-duration time constant. Other measures of motor axon excitability were not different among MJD and normals, whereas ALS patients had greater threshold changes for depolarizing conditioning currents. Severe muscle cramps were associated with

a longer strength duration time constant. Mexiletine provided almost complete relief in 8 of 10 MJD patients treated for severe muscle cramps, concomitantly improving the strength duration time constant, consistent with the premise that increased persistent Na+ conductance is causative of muscle cramps in MJD. Two patients were unable to tolerate the medication due to nausea and diarrhea. Other motor axon excitability measurements remained unchanged. Muscle cramps in MJD may have a different etiopathogenesis from those in ALS, the former involving dysfunction of Na+ channels, the latter of K+ channels. Mexiletine is a safe and beneficial treatment for these disabled MJD patients.

COMMENTARY

Where along the motor unit do muscle cramps begin? Roeleveld and colleagues[1] used a 64-channel surface electromyogram (EMG) of the triceps surface to study the initiation and development of this phenomenon; 8 cramp-prone subjects were examined during both cramp and maximal voluntary contraction (n = 4) or during cramp alone (n = 4).[1] Spectral analysis was used to interpret the information regarding the firing process and shape of the motor unit potentials.

Cramp initiation varied widely both within and between subjects, even beginning simultaneously in several locations in the muscle and spreading out slowly. Generation of the action potential appeared to occur at the level of the terminal motor axon or muscle fiber itself, rather than in the spinal cord, given that it appeared as contraction of a slowly moving fraction of muscle fibers. Compared to maximal voluntary contraction, spectral analysis revealed extremely short potentials during cramp, again supporting a nerve terminal or muscle fiber origin of cramps, rather than an origin in the anterior horn cell or more proximally along the axon.

— MICHAEL RUBIN

Reference

1. Roeleveld K, et al. *J Appl Physiol*. 2000;88:1698-1706.

Rapid Parkinsonism Follows 20% of Cirrhosis

ABSTRACT & COMMENTARY

Source: Burkhard PR, et al. Chronic parkinsonism associated with cirrhosis. *Arch Neurol*. 2003;60:521-528.

THE NEUROLOGICAL MANIFESTATIONS OF CHRONIC cirrhosis and hepatic failure are protean. Myoclonus (often negative), chorea, and dystonia may occur in these patients, often accompanied by pyramidal dysfunction and dementia. More than three-quarters of patients with chronic cirrhosis have abnormalities in the basal ganglia on MRI, typically bilateral pallidal hyperintensity on T1 images. Other studies have shown that patients with cirrhosis develop manganese deposits in the basal ganglia. The density of D2-receptors is depressed as well.

Burkhard and colleagues have studied all consecutive patients with cirrhosis who were evaluated as candidates for liver transplantation over a 1-year period in the University Hospital of Switzerland. A total of 51 patients were evaluated, and 11 were found to have clinical parkinsonism with extrapyramidal symptoms and signs. Those 11 were then carefully examined using a battery of tests that included the Unified Parkinson's Disease Rating Scale (UPDRS), a neuropsychological exam, an MRI (interpreted by a neuroradiologist blinded to patients' status), and measurements of copper and whole blood manganese. Cerebrospinal fluid levels of manganese were determined in 3 patients.

The clinical picture of cirrhosis-induced parkinsonism was very uniform. In the 11 patients, symptoms of parkinsonism began slowly and progressed rapidly over an average of 7 months. Symptoms and signs were symmetric, with generalized bradykinesia, dysarthria, postural instability, and prominent action tremor (not rest tremor). Six patients exhibited dystonia, typically involving the face and/or the feet. Mental status was reasonably preserved, but frontal lobe dysfunction developed on neuropsychological testing. Two patients were treated with levodopa, with significant improvement in parkinsonism as measured by the UPDRS. In all 11 patients, whole-blood manganese levels were elevated above normal. Cerebrospinal fluid manganese levels were also elevated in the 3 patients in whom it was measured. All patients had an abnormal MRI, with bilateral symmetric T1 hyperintensities in the substantia nigra and globus pallidus.

COMMENTARY

In this careful study, Burkhard et al have defined the clinical and radiologic features of parkinsonism associated with cirrhosis. The disorder is common and probably under-recognized. The clinical presentation is one of a rapid, progressive, symmetric parkinsonian state, unaccompanied by pyramidal dysfunction, cerebellar signs, or cognitive decline. Involvement of the substantia nigra on MRI contributes a partial presynaptic deficit in these patients, as does the response to treatment with levodopa.

The etiology of cirrhosis-induced parkinsonism is unknown, but Burkhard et al's results argue that the role of abnormal manganese deposition may be a critical factor. Unlike patients with acute manganism, neuropsychiatric features were absent in this cohort, save for evidence of frontal lobe dysfunction. Manganese deposition in the substantia nigra and globus pallidus has been previously demonstrated in patients with acute manganism. Liver transplantation in cirrhotic patients reverses the abnormalities seen on MRI. These factors suggest that manganese deposition causes cirrhotic parkinsonism. For patients who might not qualify for liver transplant, chelating agents might provide an alternate treatment to help slow this process. It certainly seems worthwhile treating these patients with levodopa. This disorder thus provides a compelling example of an extrapyramidal syndrome resulting indirectly from a serious medical illness. **— STEVEN FRUCHT**

Late Breakers

Show Stopper

A new oral direct thrombin inhibitor—ximelagatran (Exanata; Astra-Zeneca)—steals the stage at this year's American College of Cardiology 52nd Scientific Session in Chicago. Data from the SPORTIF III (Stroke Prevention Prophylaxis Using an Oral Thrombin Inhibitor in Atrial Fibrillation) trial was presented at a Late Breakers session April 9, 2003. The SPORTIF III trial was an open-label trial conducted at 259 centers worldwide, enrolling 3407 patients with nonvalvular atrial fibrillation and at least 1 other additional stroke risk factor. Patients were randomized to receive either warfarin at a dose adjusted to maintain the INR between 2.0 and 3.0 or ximelagatran in a fixed dose of 36 mg twice per day. In the noninferiority, intention-to-treat analysis, the primary end point compared the rates of all strokes (ischemic and hemorrhagic) and systemic thromboembolic events. The mean follow-up time was 17 months. There were 56 events or 2.3% events per year in the warfarin-treated group compared to 40 events or 1.6% events per year in the ximelagatran-treated arm. Though powered to only show "noninferiority," the observed risk reduction of 30% was not statistically significant but trended in favor of ximelagatran. Importantly, major and minor bleeding episodes were statistically fewer in the ximelagatran arm as well (25.5% vs 29.5%; P = .007). Liver enzyme elevations (3 times normal) were notable: 6.5% ximelagatran vs 0.7% warfarin. Though 1.2% of subjects were discontinued from the trial as protocol withdrawals due to these elevated LFTs, there was complete resolution of liver functions within 2-6 months in the remaining patients.

Ximelagatran represents a potentially major therapeutic advance. Since it is still in development (phase III/pre-NDA), we do not have a lot of pharmacokinetic and pharmacodynamic details. However, what we do know is compelling. It would represent the first new oral anticoagulant in 50 years. It is a direct thrombin inhibitor that is given in a fixed dose requiring no titration and no anticoagulation monitoring. It was a prompt onset and offset. At this point, no serious drug-drug interactions have been reported. It is estimated that 45% of afib patients at significant risk for stroke do not use anticoagulants, namely warfarin, for reasons of safety and noncompliance. If the liver enzyme elevations prove to be transient and the bleeding safety and efficacy profile remains as seen in the current SPORTIF III trial, ximelagatran will be a great addition to the neurologist/cardiologist drug armamentarium. Stayed tuned for the result of SPORTIF V, scheduled to be presented at the American Heart Association meetings in the fall of 2003.

COX-IIs for Migraine

NSAIDS represent a standard for mild-to-moderate migraine treatment. Given the overuse potential of these drugs in chronic migraine patients and the safety advantages of COX-II selective inhibitors, the use of these new drugs for migraine has been inevitable but heretofore without controlled data. At the AAN meetings this year, Silberstein presented the results of a double-blind, placebo-controlled, parallel group study comparing Vioxx 25 mg (n = 183) , 50 mg (n = 192), and placebo (n = 192) in patients with moderate-to-severe migraine (*Abstract S42.003*). On the primary end point of migraine pain relief at 2 hours, 54% (25 mg) and 57% (50 mg) experienced symptom reduction compared to 34.3% (placebo) in the placebo-treated group (P < .001). The Vioxx treated groups also achieved better 24-hour sustained pain-free response (33.5 and 37.4% vs 17.1%; P = .001).

At the Cornell Headache Service, the standard acute migraine abortive regimen includes a potent oral triptan, a COX-II inhibitor and antiemetic. While admittedly there are no head-to-head data comparing generic NSAIDS and COX-IIs and the cost deferential is significant, I believe the better safety profile and the convenience of once-daily dosing makes the COX-IIs a compelling first-line choice. **— JEFFREY REICH**

Hydroxyurea and HbF in Sickle Cell Disease

ABSTRACTS & COMMENTARY

Sources: Steinberg MH, et al. Effect of hydroxyurea on mortality and morbidity in adult sickle cell anemia. Risks and benefits up to 9 years of treatment. *JAMA*. 2003;289:1645-1651; Weiner DL, Brugnara C. Editorial: Hydroxyurea and sickle cell disease. A chance for every patient. *JAMA*. 2003;289:1692-1694.

In patients with sickle cell anemia (SCA), increasing the levels of fetal hemoglobin (HbF) decreases sickle cell hemoglobin polymerization and erythrocyte sickling. In SCA, HbF levels are inversely related to mortality.[1] The discovery that hydroxyurea, a myelosuppressive agent, increased levels of HbF in SCA patients led to the Multicenter Study of Hydroxyurea (MSH) in sickle cell anemia.[2] In MSH, 299 adults with SCA randomly were assigned to receive hydroxyurea (n = 152) or placebo (n = 147) and were followed up for a mean of 21 months. In the hydroxyurea group, morbidity was reduced by nearly half, but there was no difference in mortality or the incidence of stroke.

In the present study, Steinberg and colleagues report follow-up information on 233 of 299 patients from the MSH for up to 9 years. Upon completion of the original MSH trial, patients receiving or not receiving hydroxyurea were no longer randomized: Patients could start, stop, or continue taking hydroxyurea. Therefore, all but 47 of 233 patients were taking hydroxyurea for at least some part of the follow-up period.

Mortality rates were analyzed in 3-month intervals based on hydroxyurea use and cumulatively over 9 years.

Mortality was reduced 40% for patients taking hydroxyurea. Cumulative mortality at 9 years was 28% when HbF levels were lower than 0.5 g/dL compared with 15% when HbF levels were 0.5 g/dL or higher (P = .03). Mortality was greatest in patients with hemoglobin concentrations lower than 9g/dL and reticulocyte counts less than 250,000/mm^3. Mortality was not associated with neutrophil count. There was no difference in the occurrence of strokes between the 2 groups: There were 8 strokes in the original hydroxyurea group and 6 in the original placebo group. Eleven of the stroke patients had more than 1 year of exposure to hydroxyurea, 2 had less than 1 year of exposure, and 1 patient had unknown exposure prior to the event.

Three patients developed cancer, one each of cervical, breast, and uterine cancer; all had taken hydroxyurea for some period of time.

COMMENTARY

The results of this follow-up study suggest that adults with moderate-to-severe SCA who take hydroxyurea have reduced mortality compared with patients not taking this drug. The precise mechanism for the increase in levels of HbF induced by hydroxyurea in SCA is not known. In their editorial, Weiner and Brugnara point out that hydroxyurea increases levels of nitric oxide (NO) both in vitro and in vivo. An absolute or functional deficiency of NO, defective NO-dependent mechanisms, or both may underlie some of the physiologic disturbances of sickle cell disease since NO is a central regulator of vascular tone, cytokines, platelet aggregation, thrombosis, endothelial red cell, and leukocyte adhesion, among other mechanisms.

The demonstration that hydroxyurea benefits adult SCA patients means that pediatricians and neurologists need to carry out similar treatment trials in children with SCA who have had or are at risk for stroke. More studies are needed to determine how and when to substitute hydroxyurea for chronic transfusion therapy, which at present is the best means of reducing cerebrovascular events in children with SCA.[3,4] There is no reason to doubt that the use of hydroxyurea should and will be expanded in SCA patients of all ages.

— JOHN J. CARONNA

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2. Charache S, et al. *N Engl J Med*. 1995;332:1317-1322.
3. Adams RJ, et al. *N Engl J Med*. 1998;339:5-11.
4. Ware RE, et al. *Blood*. 1999;94:3022-3026.

Prothrombotic Factors are Highly Associated with Cerebral Venous Sinus Thrombosis

ABSTRACT & COMMENTARY

Source: Cakmak S, et al. Cerebral venous thrombosis: Clinical outcome and systemic screening of prothrombotic factors. *Neurology*. 2003;60:1175-1178.

Cerebral venous thrombosis (CVT) is a stroke syndrome characterized by headache, seizures, and hemorrhagic infarction. Compared with conventional

ischemic stroke, CVT has an excellent prognosis, especially when it is recognized rapidly with early initiation of anticoagulant therapy. CVT may be associated with a known hypercoagulable state such as malignancy or with certain exposures, such as the combination of cigarette smoking and oral contraceptive use. Infections such as chronic mastoiditis may precipitate CVT, a phenomenon known as "otitic hydrocephalus." Pregnancy and the postpartum state also elevate CVT risk.

Cakmak and associates report a series of 16 patients with CVT with an aim toward identifying underlying prothrombotic factors. Outcome, as expected, was generally excellent (in 87.5% of patients), even in the setting of hemorrhagic infarction at presentation. More interestingly, 9 of 12 patients were found to have an identifiable hypercoagulable factor. An elevated factor VIII level (with a functional level > 150%) was diagnosed in 8 of these 9. This was even more notable in that factor VIII levels were only measured in 11 of the 16 patients. Of note, 3 patients developed CVT after treatment with corticosteroids for multiple sclerosis or optic neuritis, each undergoing lumbar puncture as part of their prior workup. CSF hypotension and steroids are noted by Cakmak et al as possible contributors to CVT in these cases.

COMMENTARY

It has been well demonstrated (but perhaps not that widely recognized) that elevations in factor VIII levels increase the risk of venous thromboembolism. Factor VIII levels above the 90th percentile increase DVT and PE risk by as much as 14-fold.[1] Factor VIII appears to be a similarly potent risk factor for cerebral venous clotting, along with other newly recognized factors such as the G20210A prothrombin gene polymorphism and factor V Leiden. These data on factor VIII suggest that with ongoing advances in molecular genetics, there may soon be no such thing as an "idiopathic" venous clot.

Even in the absence of a positive finding on hypercoagulable workup, patients who have had a DVT or PE may have nevertheless "declared" themselves as an at-risk subject. Recent data suggest that long-term treatment with warfarin (at low dose and possibly at full levels) may be indicated in patients with DVT or PE regardless of whether they have a hypercoagulable state.[2]

Despite these data, it is less clear how these venous phenomena apply to arterial clot, such as in cryptogenic stroke, where platelet aggregation may play an important role. Warfarin therapy may be beneficial in selected cases of cryptogenic stroke, but this hypothesis has never been demonstrable in any large-scale randomized trial. — **ALAN Z. SEGAL**

References

1. Kyrle PA, et al. *N Engl J Med*. 2000;343:457-462.
2. Ridker PM, et al. *N Engl J Med*. 2003;348:1425-1434.

Immunosuppression, IVIG, and Diabetic Lumbosacral Plexopathy

ABSTRACT & COMMENTARY

Source: Zochodne DW, et al. Failure of immunotherapy tp prevent, arrest or reverse diabetic lumbosacral plexopathy. *Acta Neurol Scand*. 2003;107:299-301.

Intravenous immunoglobulin (IVIG) is an expensive but powerful and useful therapeutic tool in the neurologist's armamentarium. Guillain-Barré syndrome, chronic inflammatory demyelinating polyneuropathy, multifocal motor neuropathy, Lambert-Eaton myasthenic syndrome, and dermatomyositis have all been shown, in controlled clinical trials, to benefit from IVIG. Recurrent shortages of IVIG, however, underscore the notion that IVIG is being overused in instances where science has yet to document its use. Diabetic plexopathy may be one of those instances.

Three male diabetics, including a cardiac allograft recipient on cyclosporine and mycophenolate mofetil (CellCept) for immunosuppression, developed asymmetric proximal leg pain, weakness, atrophy, and areflexia consistent with a diagnosis of diabetic lumbosacral plexopathy. Nerve conduction studies and electromyography supported the diagnosis. Imaging studies, including MRI and computerized tomography of the lumbar spine, failed to demonstrate any secondary confounding structural lesion. IVIG was of no benefit in the 2 nonimmunosuppressed patients, and progression of weakness and disability occurred in all 3. Results such as these raise questions as to the use of immunosuppression for this condition and, indeed, cast doubt on whether the underlying etiology is autoimmune microvasculitis.

COMMENTARY

Proper management of these patients, as for all diabetic neuropathies, begins with strict control of hyperglycemia, which can reduce the prevalence of neuropathy by 50% at 5 years.[1] Tolrestat, an aldose reductase inhibitor (ARI), improves autonomic function and vibration perception, but ARIs alone will not likely alter the progression of neuropathy.[2] Alpha lipoic acid is current-

ly being investigated in a 4-year international multicenter trial, and interim (2-year) results are expected to be announced this month at the American Diabetes Association meeting. Gamma-linoleic acid resulted in clinical and electrophysiological improvement,[3] but human aminoguanidine trials were discontinued due to toxicity. Nerve growth factor did not deliver on its initial promise, and further trials with this agent are on hold. IVIG is appropriate and may be effective when autoimmunity underlies neuropathy, but the prevalence of neuropathy in diabetes and over-interpretation of electrodiagnostic results invite overuse. Controlled trials of IVIG for some forms of diabetic neuropathy are an idea whose time has come. **— MICHAEL RUBIN**

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2. Didangelos TP, et al. *J Diabetes Complications*. 1998;12:201-207.
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CME Questions

Please review the text, answer the following questions, check your answers against the key, and then review the materials again regarding any questions answered incorrectly. ***To receive credit for this activity, you must return a CE/CME evaluation at the end of the testing term.***

18. In Machado-Joseph disease, muscle cramps:

a. appear to have the same underlying pathogenesis as in ALS.
b. respond well to mexiletine.
c. occur rarely.
d. occur in the same frequency as they do in other patients with chronic axonal peripheral neuropathy or spinal muscular atrophy.
e. None of the above

19. In SCA patients treated with hydroxyurea improved survival correlated with which one of the following?

a. Absence of cancer
b. Absence of stroke
c. HbF 0.5g/dL or higher
d. Neutrophil count below 5000 mm^3
e. None of the above

Answers: 18 (b); 19(c)

In Future Issues:

Congenital Myasthenia and ChAT