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Amantadine for Painful Diabetic Neuropathy

ABSTRACT & COMMENTARY

Source: Amin P, Sturrock ND. A pilot study of the beneficial effects of amantadine in the treatment of painful diabetic peripheral neuropathy. *Diabet Med*. 2003;20:114-118.

ALMOST ALL PATIENTS WITH DIABETES EVENTUALLY DEVELOP neuropathy. New therapeutic options for the control of painful diabetic neuropathy are constantly being investigated. Many agents are effective, including anticonvulsants, tricyclic antidepressants (TCA), serotonin reuptake inhibitors, and analgesics. None work in all patients, and all have unwanted side effects. Amantadine, a non-competitive N-methyl-D-aspartate (NMDA) antagonist, is the latest agent to show promise.

Twenty diabetic neuropathy patients were randomized into a double-blind, placebo-controlled, crossover trial of 200-mg intravenous amantadine infused once weekly for 2 weeks following an initial 28-day analgesic wash-out period and a single placebo infusion. Type 1 or type 2 diabetics were eligible and had at least 6 months of painful diabetic neuropathy diagnosed clinically with or without abnormal electrodiagnostic studies. Exclusionary criteria included other causes of peripheral neuropathy, renal insufficiency, pregnancy, prostatism, or psychiatric history. Outcome measurements comprised a 100-mm visual analogue scale for pain intensity and pain relief, the Neuropathy Symptom Score, and Physician's Global Evaluation. Statistical analysis was provided by Student's t-test.

Seventeen patients completed the study; a foot ulcer, a transient ischemic attack, and the need for opiates excluded 1 patient each. Most were male (n = 9), type 2 diabetic (n = 15), and Caucasian (n = 16), with a mean duration of diabetes for 21 years and neuropathy for 29 months. Mean age was 58.4 years, and prior treatments included TCA (n = 6), carbamazepine, gabapentin, or paracetamol (3 each), capsaicin or nonsteroidals (2 each), and acupuncture (n = 1). Compared to placebo, amantadine infusion resulted in significant improvement in all measured ways. Intravenous amantadine provided relief from painful diabetic neuropathy, and the improvement was sustained for at least 1 week following infusion.

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INSIDE

COMMENTARY

Hyperglycemia, the clear and proximate antecedent of diabetic neuropathy, sets off a plethora of metabolic abnormalities leading to oxidative stress and mitochondrial malfunction, resulting in neuronal and Schwann cell apoptosis and consequent neuropathy.[1] Metabolic abnormalities include enhanced aldose reductase activity with resultant sorbitol and fructose accumulation and myoinositol depletion in nerve. Protein kinase C is inappropriately activated, advanced glycation end products are produced, and oxygen free radicals are generated. Diabetic neuropathy is multifactorial.

Hedgehog (Hh) proteins, including sonic, desert, and indian Hh protein, are crucial for normal nervous system development—sonic Hh (SHh) protein in the central nervous system and desert Hh (DHh) protein in the peripheral nervous system. DHh is found only in Schwann cells, and in diabetic rats DHh mRNA is reduced.[2] Complete normalization of motor and sensory nerve conduction velocities was achieved with infusion of SHh-IgG (ibid.), suggesting that therapeutic benefit may accrue from this management strategy.

Overt clinical hyperglycemia may not be a prerequisite for the development of neuropathy.[3] Among 73 patients with peripheral neuropathy of unknown cause who completed an oral glucose tolerance test, 41 (56%) were abnormal. Diabetes (defined as fasting glucose > 126 mg/dL or 2-hour postglucose challenge > 200 mg/dL) was found in 15 and impaired glucose tolerance in 26 (IGT, fasting glucose 110-126 mg/dL or 2-hour postglucose challenge 140-200 mg/dL). IGT patients predominantly suffered from small fiber neuropathy, as documented by distal leg intraepidermal nerve fiber densities and had less severe large-fiber neuropathy compared to those with diabetes. Diabetes may cause significant painful neuropathy before it is evident, and all idiopathic painful polyneuropathy patients should undergo oral glucose tolerance testing. — **MICHAEL RUBIN**

References

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3. Sumner CJ, et al. *Neurology*. 2003;60:108-111.

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Hashimoto Encephalopathy: Syndrome or Coincidence?

ABSTRACTS & COMMENTARY

Sources: Taylor SE, et al. An organic cause of neuropsychiatric illness in adolescence. *Lancet*. 2003;361:572; Chong JY, et al. Hashimoto encephalopathy. Syndrome or myth? *Arch Neurol*. 2003;60:164-171.

TAYLOR AND ASSOCIATES REPORT A CASE OF Hashimoto encephalopathy in an adolescent girl with a 9-month history of what was initially diagnosed as chronic fatigue syndrome. Her illness included episodic neurological symptoms (altered consciousness, mild cognitive impairment, tremor, myoclonus, and a generalized seizure) as well as psychiatric features (mood swings, panic attacks, delusions, and hallucinations). The only abnormal laboratory tests were raised antithyroid microsomal antibodies and weakly positive antinuclear antibodies. EEG showed diffuse background slowing, and CSF protein was elevated (57 mg/dL). All symptoms resolved within 3 days of starting intravenous glucocorticosteroids in high dosage. Therefore, Taylor et al recommend that chronic fatigue syndrome be diagnosed with caution in adolescents, especially when there are associated neurologic signs and psychopathology. In such cases, Hashimoto encephalopathy should be a diagnostic consideration.

Chong and colleagues report a 63-year-old woman whose subacute onset of cognitive impairment, ataxia,

Table 1.

Hashimoto Encephalopathy: Clinical Features in 85 Patients

Clinical Feature	Patients	
	n	(%)
Focal Deficit	23	27
Seizures	56	60
Psychosis	31	36
Relapsing-Remitting Course	51	60
High CSF ProteinConcentration	66	78
Abnormal Brain Imaging	40/82	49
Abnormal EEG	80/82	98
Response to Glucocorticoids	67/70	96

Table 2.

Thyroid Dysfunction in 85 Patients

Category	n	%
Euthyroid	26	31
Hypothyroid	48	56
Hyperthyroid	6	7
Not Reported	5	6
Anti-M[1] present	55/58	95
Anti-TPO[2] present	26/26	100
Anti-Tg[3] present	45/62	73

References

1. Antithyroid microsomal antibody
2. Antithyroid peroxidase antibody
3. Antithyroglobulin antibody

and headache prompted a diagnosis of viral encephalitis. Symptoms improved with empirical antiviral treatment, but some months later she developed increasing confusion, tremor, generalized seizures, and coma. Brain MRI showed diffuse, nonenhancing white matter hyperintensity. There was a CSF leukocytosis of 26 cells per mm^3, and the CSF protein was 98 mg/dL. Brain biopsy was nondiagnostic. A diagnosis of Hashimoto encephalopathy was made on the basis of elevated serum antithyroid microsomal antibody concentrations. The patient gradually improved with chronic glucocorticoid therapy and was neurologically normal 15 months later.

In a review of the literature, Chong et al identified 85 patients with encephalopathy and high serum antithyroid antibody concentrations (*see Table 1*). The mean age at onset was 44 years (range, 9-78 years). Nineteen were boys or girls 18 years or younger. Among the adults, there were 53 women and 13 men.

Neurologic symptoms were similar in all patients whether they were euthyroid, being treated with levothyroxine, or were hypothyroid. Serum concentrations of thyroid antibodies varied widely, and there was no relationship between neurologic symptoms and signs and the type or serum concentration of antithyroid antibodies (*see Table 2*).

Based on their review of cases of Hashimoto encephalopathy, Chong et al concluded that the constellation of clinical manifestations constitutes a syndrome and that high serum antithyroid antibody concentrations are unlikely to be a chance association.

COMMENTARY

Hashimoto encephalopathy is associated with high serum antithyroid antibody concentrations, but there is no evidence that these antibodies have a role in the pathogenesis of the cerebral disease. Chong et al point out that patients with autoimmune disease often have high serum concentrations of one or more antibodies directed against tissues not affected by the particular autoimmune disease. Therefore, the presence of high serum antithyroid antibody concentrations in Hashimoto patients could be another example of this autoimmune phenomenon, rather than indicating that the antibodies have a causal relationship to the encephalopathy.

One can conclude, however, that Hashimoto encephalopathy is a distinct clinical syndrome that is identified by and linked to the presence of high serum antithyroid antibody concentrations. — **JOHN J. CARONNA**

Gluten Ataxia: Fact or Fiction?

ABSTRACT & COMMENTARY

Source: Hadjivassiliou M, et al. Gluten ataxia in perspective: Epidemiology, genetic susceptibility and clinical characteristics. *Brain*. 2003;126:685-691.

This population report investigated the prevalence of gluten sensitivity amongst a large cohort of patients with both sporadic and familial ataxia. Hadjivassiliou and associates studied 224 patients with various causes of ataxia from North Trent in England. Fifty-nine of the patients had known genetic causes, including either spino cerebellar ataxias or Friedreich's ataxia. A total of 132 of the patients had sporadic idiopathic cerebellar degeneration, and 33 had a clinically probable cerebellar variant of multiple system atrophy. An additional 44 patients with sporadic idiopathic ataxia from

the Institute of Neurology in London were screened for the presence of antigliadin antibodies. A total of 1200 volunteers were screened as normal controls. The prevalence of antigliadin antibodies in the normal controls was 12%. In the patients with familial ataxia, it was 14%. It was 41% in the sporadic idiopathic group and 15% in the multiple system atrophy group. In the patients from London, antigliadin antibodies were present in 14 out of 44. The clinical onset in patients with presumed gluten ataxia occurred at a mean age of 48 years, and the mean duration of ataxia was 9.7 years. Gait ataxia occurred in all patients. The patients had ocular signs in 84% and dysarthria in 66%; upper limb ataxia was evident in 75% and lower limb ataxia in 90%. Gastrointestinal symptoms were present only in 13%. The MRI scans showed atrophy of the cerebellum in approximately 80%. Nerve conduction studies showed a sensorimotor axonal neuropathy in 45% of the patients. Gluten-sensitive enteropathy was present in 24% of the patients, and the HLA DQ2 genotype was present in 72% of patients. Hadjivassiliou et al concluded that gluten ataxia is the most single common cause of sporadic idiopathic ataxia.

COMMENTARY

This paper contributes to an increasing body of evidence that suggests that gluten sensitivity may contribute to a number of neurologic syndromes. Gluten sensitivity is most commonly recognized as a chronic diarrheal illness with bloating and progressive weight loss, known as coeliac disease. It is also associated with a number of other conditions, including dermatitis herpetiformis, IgA deficiency, IgA nephropathy, Sjogren syndrome, autoimmune thyroid disease, type 1 diabetes, rheumatoid arthritis, and Down's syndrome.

Most prior studies of gluten-associated ataxia have been small with limited numbers of patients. Two studies were published in 2001. In 1 American study, the prevalence of antigliadin antibody positivity in both sporadic and familial ataxias was 27% and 37%, respectively.

In a larger study from Germany, the prevalence of gluten ataxia among sporadic idiopathic ataxias was found to be 12 out of 104 (11.5%).[1] In this population, the prevalence of IgG antigliadin antibodies amongst normal controls was 5%. Of the 12 patients, 2 had typical changes of gluten sensitive enteropathy, and 5 had an elevated interepithelial lymphocyte count. Five patients had no evidence of any abnormal biopsied gastrointestinal abnormalities. In this study from Germany, the link with HLA DQ2 hepatype was 70%. The symptoms were noted not to be related to low blood concentrations of vitamins, particularly vitamin E. Previously, ataxia associated with coeliac disease had been suggested as a consequence of vitamin E deficiency, and some patients responded to vitamin E supplementation. This is plausible, since patients with mutations in the alpha-tocopherol binding protein are known to have low vitamin E levels and to develop progressive cerebellar ataxia. In the German study, the clinical syndrome was dominated by progressive cerebellar ataxia of stance and gait, as well as dysarthria and limb ataxia. The symptoms, however, were relatively mild. One feature that has been found both in the present study as well as in the German one is frequent loss of posterior column sensation, as well as bladder dysfunction and reduced ankle reflexes. In the German study, a prominent axonal neuropathy with reduced amplitudes and abnormal evoked potentials affected about 50% of the patients. All patients showed cerebellar atrophy on MRI. CSF studies were normal.

A critical issue is the nature of antibodies and screening for sporadic ataxia in patients. Some patients with putative gluten ataxia have IgG antigliadin antibodies, whereas most commonly IgA antibodies are found during routine screening. More specific antibodies are those against antiendomysium, which correlate well with coeliac disease but lack sensitivity and specificity when used in screening patients with ataxia. In the present study, the IgG antigliadin antibody was the best marker of gluten sensitivity. The clinical findings of ataxia in these groups of patients do not allow one to separate these patients from other patients with sporadic ataxia. There is a paucity of neuropathologic reports from patients with gluten ataxia. Only 2 patients have been studied who showed some perivascular cuffing with CD4 and CD8 cells, as well as patchy loss of Purkinje cells.

The finding of a strong association with certain HLA and inflammatory changes makes it likely that these patients are suffering from an immune-mediated cerebellar degeneration. This may be similar to the antibodies that occur in paraneoplastic cerebellar degeneration, such as the anti-Yo antibody. The major difficulty with identifying gluten ataxia is the high prevalence of antigliadin antibodies in the normal population.

It is unclear whether a gluten-free diet has efficacy in these patients. Most of them identified and have had disease of long duration, making it too late to intervene. It has been reported that resolution of symptoms with a gluten-free diet might be in patients diagnosed early. It is worthwhile to screen antigliadin antibodies in patients with sporadic ataxia at their initial presentation. If positive, consider a gluten-free diet since at present, there are no other effective treatments for sporadic cerebellar ataxias. At present, the entity of gluten ataxia warrants

further investigation to establish its pathophysiology, more reliable screening tools, and the efficacy of gluten-free diets. — **M. FLINT BEAL**

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1. Burk K, et al. *Brain*. 2001;124:1013-1019.

Muscle Biopsy in Benign HyperCKemia

ABSTRACT & COMMENTARY

Source: Simmons Z, et al. Muscle biopsy in the evaluation of patients with modestly elevated creatine kinase levels. *Muscle Nerve*. 2003;27:242-244.

BENIGN HYPERCKEMIA MAY BE DEFINED AS SERUM elevation of creatine kinase (CK) in an asymptomatic patient or in a patient with nonspecific symptoms, including muscle pain, fatigue, cramps, stiffness, normal neurological examination, and normal or nondiagnostic electrodiagnostic (nerve conduction studies and electromyography) studies. Rarely does a treatable disorder underlie such CK elevation, and the use of muscle biopsy remains questionable.

Over a 9-year period, 20 patients, 14 men and 6 women, demonstrated modest serum CK elevation (< 1000 U/L) on at least 2 occasions with no history of myoglobinuria. All had normal muscle strength, negative family history for neuromuscular disease or malignant hyperthermia, and nondiagnostic EMG studies. All underwent biopsy with extensive evaluation of the tissue to determine if such studies contributed to their diagnosis and treatment. Muscle stains included hematoxylin-eosin, Gomori trichrome, oil-red-O, periodic acid-Schiff, adenosine triphosphatase, succinate dehydrogenase, NADH-tetrazolium reductase, cytochrome oxidase, myophosphorylase, myoadenylate deaminase, and stains for dystrophin, sarcoglycans, laminin (merosin), and dysferlin. Absent a diagnosis by these techniques, biochemical analysis was pursued, including phosphorylase, phosphorylase b kinase, phosphofructokinase, phosphoglycerate kinase, phosphoglycerate mutase, lactate dehydrogenase, and carnitine palmitoyltransferase.

Myoadenylate deaminase deficiency was demonstrated in 1 patient. In the remainder, biopsy was normal in 9, nonspecific in 6 (minor muscle fiber atrophy and fiber type predominance), and mildly myopathic in 4 (rare degenerating or regenerating fibers, internal nuclei, or split fibers). Immunohistochemistry was normal in all. Biochemically, phosphorylase b kinase was deficient in 3 and carnitine palmitoyltransferase in 2. Neither muscle biopsy findings nor biochemical abnormalities predicted an abnormality in the other. Extensive evaluation of muscle biopsy in benign CK elevation is warranted for diagnostic purposes but will not alter patient management.

COMMENTARY

Among 114 patients with benign hyperCKemia, a diagnosis of disease was made in 18.4%, with nonspecific skeletal muscle abnormalities found in 38.6% and completely normal muscle biopsy findings in 31.6%.[1] Long-term follow-up of 31 such patients revealed that although symptoms tend to persist with no substantial change in myalgia or fatigue, deterioration is not seen.[2] Importantly, even in the absence of established myopathy, such patients may be at risk for malignant hyperthermia, as demonstrated by in vitro sensitivity to caffeine.[3] Patients must be so informed. Elevation of CK is well recognized following exercise. Such elevation is less pronounced in well-trained athletes as compared to untrained persons.[4] Despite serum elevation, athletes were asymptomatic for muscle pain or chest discomfort. — **MICHAEL RUBIN**

References

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New Treatment for Overactive Bladder

ABSTRACT & COMMENTARY

Source: FDA Center for Drug Evaluation and Research. www.fda.gov/cder/approval.

ON FEBRUARY 26TH, THE FDA APPROVED A transdermal formulation of oxybutynin for the treatment of overactive bladder and urinary incontinence. Oxytrol Patch (Watson Pharmaceuticals) provides 3.9 mg/d and can be administered twice per week. The transdermal delivery avoids initial first-pass liver metabolism of the oral oxybutynin formulations and, therefore, significantly less plasma concentration of the active n-desethylooxybutynin metabolite.

With less active metabolite, the sponsoring company has argued that the anticholinergic profile is superior to the

oral formulation. The label includes results from 2 phase 3 studies. The first compared the patch to placebo, and the second trial looked at the patch in reference to standard oral therapy. This study was a 12-week, double-blind, double-dummy, placebo-controlled trial with 361 patients, randomized into 3 treatment arms—1 arm received the 3.9 mg/d patch twice weekly, another received 4 mg of Detrol LA daily, and the last received placebo. Subjects were required to have at least 4 urge incontinent episodes and at least 24 voids (of less than 350 cc) as recorded in a 3-day diary during the baseline phase of the study. The primary end point for the study was the change in the number of incontinent episodes. The preliminary results show that Oxytrol and Detrol LA both reduced incontinent episodes by 62% and 64%, respectively, compared to the 42% decline from baseline in the placebo population ($P < .001$). In terms of side effects, dry mouth from the Detrol LA was 7.4%, which was statistically different from the placebo rate of 1.7% ($P < .001$). The 4.7% incidence of dry mouth with the Oxytrol Patch was not statistically different. However, the Oxytrol Patch did show an 18% incidence of skin irritation. This was not enough of a problem to warrant discontinuation of the drug. Watson plans to publish the full results in mid-2003.

COMMENTARY

An alternative transdermal formulation to Ditropan XL and Detrol LA for the treatment of urinary incontinence is a welcome addition to the therapeutic armamentarium. If the improved side effect profile from having less anticholinergic metabolites proves to be a real clinical advantage, the patch may find itself the preferred first-line choice. Regardless, the patch still offers significant benefits considering the special needs of some of our neurologically impaired patients. **— JEFFREY REICH**

Are GABAergic Agents Toxic to the Retina?

ABSTRACTS & COMMENTARY

Sources: Krauss GL, et al. A controlled study comparing visual function in patients treated with vigabatrin and tiagabine. *J Neurol Neurosurg Psychiatry*. 2003;74:339-343; Lawden MC. Vigabatrin, tiagabine, and visual fields. *J Neurol Neurosurg Psychiatry*. 2003;74:286.

VIGABATRIN (VGB) IS AN ANTIEPILEPTIC DRUG (AED) whose putative mechanism of action is to increase inhibitory tone in the brain by blocking the metabolism of gamma-amino butyric acid (GABA) by irreversibly binding to GABA transaminase. It is available in the European Union, Canada, and Mexico, where it is the AED of choice for treating infantile spasms associated with tuberous sclerosis. VGB is unlikely to achieve approval by the US Food and Drug Administration because up to 40% of patients treated with the drug develop concentric visual deficits, which can be permanent. While there have been case reports of tiagabine (TGB), an AED that blocks GABA reuptake by neurons and glia, causing comparable visual impairments, Krauss and colleagues are the first to undertake a controlled study to compare VGB and TGB with regard to this adverse effect.

The study design involved a cross-sectional comparison of visual acuity, color vision, Goldman and Humphrey perimetry, and electroretinograms (the effects of VGB on vision are thought to be due to retinal dysfunction) among patients taking VGB, TGB, or another AED (the control group) for at least 6 months. Thirty-two patients were treated with VGB, 12 with TGB, and 14 with another AED. Eight of the control subjects were taking an agent known to affect GABA: gabapentin, topiramate, or valproic acid. The main findings were that there were no differences between groups when looking at visual acuity or color vision. However, the VGB group had abnormal findings on kinetic (Humphrey) visual field testing and ERG that were significantly different relative to TGB and control patients.

COMMENTARY

There is extensive clinical experience with GABA agonists that bind to the barbiturate and benzodiazepine binding sites on different classes of the GABA receptor. There have been no consistent findings of visual dysfunction in patients thus treated. Rather than binding directly to GABA receptors, both VGB and TGB modulate GABAergic tone by modulating synaptic accumulation of GABA. Why, then, are there significant differences in the adverse effect profile of these 2 agents with respect to retinal function? Krauss et al cite several theories to account for this phenomenon. One hypothesis relates to the fact that VGB markedly increases the concentration of GABA in cortical astrocyte cell culture, whereas TGB does not.[1-2] These supra-physiologic GABA levels may play a role in GABAergic amacrine cell injury seen in the inner retina in pathologic specimens. There are also differences in VGB distribution in the retina relative to brain. VGB levels are 5-fold higher in rodent retina vs brain. Conversely, TGB levels are slightly reduced in retina vs brain.[3]

Clearly, not all GABA agonists are the same. The lesson of VGB vs TGB is that not all modulators of GABA reuptake and metabolism are the same, either. The latter fact is promising with respect to the rational design of drugs that modulate GABA. As Lawden concludes in the accompanying editorial to the study: "A class effect of GABAergic drugs causing retinal damage now seems unlikely." These agents are quite effective in the treatment of epilepsy. We can look forward to new AEDs currently in development that increase GABAergic tone without the retinotoxic effects of VGB. — **ANDY C. DEAN**

Dr. Dean is Assistant Professor of Neurology and Neuroscience, Director of the Epilepsy Monitoring Unit, Department of Neurology, New York Presbyterian Hospital—Cornell Campus.

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Statins for Stroke: Treating More Than Just Cholesterol

ABSTRACT & COMMENTARY

Soucre: Gertz K, et al. Withdrawal of statin treatment abrogates stroke protection in mice. *Stroke*. 2003;34:551-557.

HMG-COA REDUCTASE INHIBITORS (STATINS) ARE known to reduce the risk of myocardial infarction and stroke. Statins are effective not only as cholesterol lowering agents but also have beneficial effects on endothelial cell function, as well as antithrombotic and anti-inflammatory effects. Through upregulation of endothelial nitric oxide synthase (eNOS) and the production of nitric oxide (NO), these agents augment regional blood flow and inhibit platelet aggregation. Because much of the damage from stroke likely occurs due to a failure of the microcirculation, augmentation of small vessel flow by NO may allow greater salvage of the ischemic penumbra and an attenuation of overall infarct size.

Gertz and associates studied mice treated with atorvastatin for 14 days prior to an experimental occlusion of the middle cerebral artery. These mice were compared with vehicle treated controls. Among treated mice, serum cholesterol measurements were not affected. In 2 additional experimental groups, atorvastatin was given for 14 days and then withdrawn either 2 days (14 ± 2d) or 4 days (14 ± 4d) prior to MCA occlusion. Treated animals had a 40% reduction in infarct volume compared to vehicle-treated animals. Beneficial effects of atorvastatin were blunted in the 14 ± 2d mice and stroke volumes were equal to control in the 14 ± 4d group. Measures of eNOS production (via PCR for eNOS mRNA) and platelet activation (measured as "tail bleeding times") showed deleterious rebound effects from statin withdrawal in the 14 ± 2d mice with return to baseline at 14 ± 4d. Thrombus formation induced by ligature of the inferior vena cava was significantly reduced by statin treatment. This protection was lost in the 14 ± 2 or 4d mice.

As Gertz et al observe, existing data in humans provide strong support for these results. In studies of patients with acute coronary syndromes, statins immediately following a myocardial infarction have a marked short-term protective effect on both cardiac recurrent events and stroke. In the MIRACL trial,[1] there was a 50% reduction in stroke rates over the first 16 weeks after MI among patients on atorvastatin. This effect was independent of any cholesterol lowering.

COMMENTARY

Statins have a crucial role in the secondary prevention of stroke and should be started immediately in the hospital upon the diagnosis of cerebral infarction. Statins furthermore should be prescribed and maintained for any patient at high risk for stroke, such as those with prior TIA or known carotid artery disease. An aggressive LDL cholesterol goal of < 100 should be the target for statin therapy, and consideration for a statin should be made even for patients with lipids in this optimal range. — **ALAN Z. SEGAL**

Reference

1. Schwartz GG, et al. *JAMA*. 2001;285:1711-1718.

New Gene for Familial Parkinson's Disease Located

ABSTRACT & COMMENTARY

Source: Bonifati V, et al. Mutations in the DJ-1 gene associated with autosomal recessive early-onset parkinsonism. *Science*. 2003;299:256-259.

TEN LOCI AND GENES HAVE BEEN LINKED TO FAMILIAL Parkinson's disease, and their chromosomal location

and mode of inheritance are listed in Table 1. Mutations in α-synuclein and parkin have been described in families with Parkinson's disease, and both gene products are involved in the function of the proteosome, a major pathway for degradation of proteins within the cell. In the current report, Bonifati and colleagues report their isolation of the DJ-1 gene in 2 consanguineous, genetically isolated families in The Netherlands and Italy.

Mutations in the DJ-1 locus are responsible for PARK7 parkinsonism. DJ-1 mutations completely cosegregated with clinical phenotype in these 2 families. The DJ-1 gene contains 8 exons and encodes a 189-amino-acid protein that is widely expressed throughout the body and the brain. It is closely related to known bacterial proteases. Based on structural models of the protein, the mutation in the Italian family likely enhances the ability of the protein to aggregate as multimers. The function of DJ-1 in man is unknown. However, it is responsive to hydroperoxide and may function in the cell as an antioxidant. The possibility exists that DJ-1 functions in dopamine neurons to buffer reactive oxygen species produced by normal metabolism of dopamine.

Bonifati et al also explored the function of DJ-1 by transfecting cells in cell culture with the gene. Wild-type DJ-1-transfected cells showed that the protein is normally diffusely expressed throughout the nucleus and cytoplasm. In contrast, cells transfected with mutant DJ-1 showed cytoplasmic concentration of the protein almost completely within mitochondria.

Table 1.

The Genetics of Familial Parkinson's Disease

Locus	Chromosome	Gene	Inheritance
PARK1	4q21.3	a-synuclein	AD
PARK2	6q25	parkin	AR
PARk3	2p13	?	AD
PARK4	4p15	?	AD
PARK5	4p14	UCH-L1(?)	AD
PARK6	1p35	?	AR
PARK7	1p36	DJ-1	AR
PARK8	12p11	?	AD
PARK9	1p36	?	AR
PARK10	1p32	?	?

Adapted from Dawson and Dawson. *J Clin Investigation*. 2003;111: 145-151.

COMMENTARY

This report documents the third major locus for genetic forms of Parkinson's disease. To date, all identified genes are involved in the proteosome system or in cascades that modulate oxidative stress within the cell. Progress in the field of Parkinson genetics parallels strides made a decade ago in Alzheimer's disease. In that disease, different genetic mutations in proteins involved in processing of the amyloid precursor protein produced highly similar clinical and pathological phenotypes. The current discovery of the DJ-1 gene is an important step in understanding the molecular mechanisms of nigral cell degeneration in inherited and sporadic Parkinson's disease. — **STEVEN FRUCHT**

Correction

CME question No. 6 in the March 2003 issue had 2 correct answers. This question will be eliminated.

CME Questions

10. In diabetes mellitus:

a. neuropathy does not develop before overt hyperglycemia is evident.
b. sorbitol and fructose are depleted and myoinositol accumulates in nerve.
c. amantadine infusion appears to be not significantly better than placebo for the treatment of painful diabetic neuropathy.
d. Indian hedgehog protein is reduced in Schwann cells of diabetic rats.
e. None of the above

11. Which of the following statements is *false*? Hashimoto encephalopathy:

a. occurs in children and adults.
b. is more frequent in women.
c. is associated with seizures.
d. is caused by antithyroid antibody-mediated cerebral damage.
e. is responsive to treatment with glucocorticoids.

12. Benign hyperCKemia defined as serum elevation of creatine kinase (CK) in asymptomatic persons:

a. is due to underlying myositis in the majority.
b. is rarely if ever associated with diagnostic pathology on muscle biopsy.
c. EMG will usually reveal a specific diagnosis.
d. is usually a benign disorder.
e. None of the above

Answers: 10(e); 11(d); 12(d)

In Future Issues:

NSAIDS: Not Protective vs Ischemic Stroke