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## INSIDE



# Natalizumab Receives Accelerated FDA Approval For MS

SPECIAL UPDATE

***Synopsis:*** *Natilizumab will become an important option for newly diagnosed MS patients starting treatment, or for patients currently on interferon beta-1a or glatiramer acetate with refractory breakthrough disease.*

BIOGEN IDEC AND ELAN CORPORATION RECEIVED FDA APPROVAL for natalizumab in the treatment of relapsing-remitting MS on November 23, 2004. One-year data from the Phase III TYSABRI® (natalizumab) AFFIRM trial met the primary end point of clinical relapse rate reduction. In this international study of 942 patients with relapsing-remitting multiple sclerosis (RRMS), natalizumab significantly reduced the rate of relapses by 66%, compared to placebo. All secondary end points for brain MRI were also met.

Natalizumab is a humanized monoclonal antibody against the alpha-4 integrin selective adhesion molecule (SAM), which blocks the attachment to the corresponding VCAM receptor on the vascular endothelium of the blood-brain barrier. This limits the trafficking of activated T-cells into the nervous system.

The AFFIRM trial is a 2-year, randomized, multi-center, placebo-controlled, double-blind study of 942 patients evaluating the effect of natalizumab monotherapy on the progression of disability in MS and the rate of clinical relapses. An annualized relapse rate of 0.25 was seen with the natalizumab-treated patients vs 0.74 with placebo-treated patients. The proportion of patients who remained relapse free was 76% in treated patients, compared to 53% in the placebo group ($P < 0.001$). Secondary end points at 1 year included the number of new or newly enlarging T2-hyperintense lesions, the number of gadolinium-enhancing lesions, and the proportion of patients who were relapse free. On 1-year data, 96% of natalizumab-treated patients had no gadolinium-enhancing lesions, compared to 68% of placebo-treated patients ($P < 0.001$). To enroll, patients had to be diagnosed with a relapsing form of MS and had to have experienced at least 1 relapse in the previous year. Patients were randomized to receive a 300 mg IV infusion of natalizumab (n = 627) or placebo (n = 315) once a month.

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Adverse events occurring in at least 5% of natalizumab-treated patients that were 2% more common than in placebo-treated patients included headache, fatigue, and arthralgia. The overall incidence of infection was similar between the groups. Serious infections occurred in 1% of placebo-treated patients and 2% of natalizumab-treated patients. Serious hypersensitivity-like reactions occurred in approximately 1% of natalizumab-treated patients. Unfortunately, a small percentage of patients who developed binding antibodies to natalizumab seemed to lose the effectiveness of drug.

A second Phase III trial now in progress, SENTINEL, is a 2-year controlled study of approximately 1200 patients with relapsing-remitting MS, evaluating the effect of the combination of natalizumab and interferon beta-1α, 30 μ IM/week (AVONEX®), compared with interferon beta-1α alone on the progression of disability and the rate of clinical relapses. At 1 year, the natalizumab plus interferon beta-1α treated group experienced a 54% reduction in the rate of clinical relapses, compared to the effect of interferon beta-1α alone. In addition, 96% of natalizumab plus interferon beta-1a treated patients had no gadolinium-enhancing lesions on MRI, compared to 76% in the interferon beta-1α plus placebo group. Sixty-seven percent of the natalizumab plus interferon beta-1α treated group remained relapse-free, compared to 46% in the interferon beta-1α plus placebo treated group.

This therapeutic strategy of selective adhesion molecule blockade may represent a significant advance in our treatment of multiple sclerosis. Natilizumab will become an important option for newly diagnosed patients starting treatment, or for patients currently on interferon beta-1a or glatiramer acetate with refractory breakthrough disease. We eagerly await the full 2-year data sets in the above clinical trials to see if benefits are sustained, and if there is any impact of natalizumab ultimately on progression of disability in multiple sclerosis.

— **BRIAN R. APATOFF**

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# Cloning of PARK8: LRRK2 in Autosomal, Dominant Late-Onset Parkinson's Disease

ABSTRACTS & COMMENTARY

***Synopsis:*** *LRRK2 may be central to the pathogenesis of several major neurodegenerative disorders associated with Parkinsonism.*

**Sources:** Paisán-Ruíz C, et al. Cloning of the Gene Containing Mutations that Cause PARK8-Linked Parkinson's Disease. *Neuron.* 2004;44:595-600; Zimprich A, et al. Mutations in LRRK2 Cause Autosomal Dominant Parkinsonism With Pleomorphic Pathology. *Neuron.* 2004;44:601-607.

Despite the rarity of familial Parkinson's disease (PD), recent identification of the genes involved has helped elucidate molecular mechanisms that may go awry in this disease. Now, a sixth gene leading to familial PD has been identified independently by 2 groups exploiting high resolution mapping techniques and sequencing of multiple candidate genes. The PARK8 locus was identified in 2002 in the Japanese Sagamihara kindred, associated with autosomal dominant inheritance of PD. The locus has since been associated with other unrelated families in Europe and North America, and individuals have a clinical phenotype of typical late-onset PD, with an excellent levodopa response. Paisán-Ruíz and colleagues identified the gene LRRK2 (leucine-rich repeat kinase 2) as that corresponding

to the PARK8 locus, in a study of 1 English and 4 Basque families. They identified 2 disease-segregating missense mutations, and if unaffected individuals under 79 years old were excluded, penetrance was 100%. Moreover, of 107 sporadic cases, 5 individuals carried one of these missense mutations. Independently, Zimprich et al analyzed 46 families, identifying 5 missense mutations (2 identical to those in the Basque and English families) and 1 putative splice site mutation in LRRK2. Over 1000 control chromosomes studied by each group had no such LRRK2 mutations. The predicted protein structure comprises 12 leucine-rich repeats, a non-receptor tyrosine kinase-like domain, a Ras/small GTPase superfamily domain, and a WD40 domain. Corresponding mRNA was detected throughout the brain, as well as other tissues including liver and cardiac muscle.

## COMMENTARY

The newly identified gene for the PARK8 locus, LRRK2, now joins alpha-synuclein and ubiquitin C-terminal hydrolase L1 (UCH-L1), the genes responsible for autosomal dominant inheritance of PD. In contrast, parkin, PTEN-induced putative kinase 1 (PINK1), and DJ-1 lead to autosomal recessive familial PD. Cloning of the gene for PARK8 also follows hot on the heels of identification of the glucocerebrosidase gene as a possible susceptibility factor for PD.[1,2] Abnormal folding, aggregation, and deposition of alpha-synuclein is thought to contribute to dopamine neuron dysfunction and demise in PD, and involvement of parkin and UCH-L1 highlight a role for cellular protein degradation via the ubiquitin-proteasome system. How PINK1 and DJ-1 mutations lead to PD is less clear, but DJ-1 is suggested to protect against oxidative damage, and identification of PINK1, a mitochondrial protein kinase, supports current concepts of mitochondrial pathology in PD. Where, then, does LRRK2 fit into this picture? As yet we can only infer function from its predicted structure, and this is complicated by identification of several quite different domain types, as noted above. It may have activity as a cytoplasmic tyrosine kinase, and one region fits a recently defined multifunctional Ras/GTPase family, termed ROCO, whose members have diverse activities including a role in cytoskeleton organization. Additionally, the presence of LRR domains suggest that LRRK2 acts as part of a protein complex. Finally, it is fascinating that PARK8 families display remarkable neuropathological heterogeneity.[3] Patterns observed to date include: neuronal loss and gliosis in the subtantia nigra with nigral Lewy bodies; pure nigral degeneration without Lewy bodies or other pathology determined; widespread Lewy body disease including the cortex; and neurofibrillary tangles in the absence of Lewy bodies. It remains to be determined whether LRRK2 mutations could therefore account for other neurodegenerative diseases with these pathologies. Moreover, understanding its function and dysfunction will broaden the scope of current possibilities for targeted therapeutic intervention. — **CLAIRE HENCHCLIFFE**

*Claire Henchcliffe, MD, is Assistant Professor in the Department of Neurology at the Weill Medical College of Cornell University.*

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3. Wszolek ZK, et al. Autosomal Dominant Parkinsonism Associated With Variable Synuclein and Tau Pathology. *Neurology.* 2004;62:1619-1622.

# A New Approach Preventing Amyloid Aggregation May Result in Novel Therapeutics For Alzheimer's Disease

ABSTRACT AND COMMENTARY

***Synopsis:*** *This strategy yields potent inhibitors of A-beta aggregation and could lead to therapeutics for Alzheimer's disease and other forms of neurodegeneration.*

**Source:** Gestwicki J, et al. Harnessing Chaperones to Generate Small-Molecule Inhibitors of Amyloid Aggregation. *Science.* 2004;306:865-871.

AGGREGATION OF THE A PEPTIDE GENERATED BY THE proteolytic cleavage of the amyloid precursor protein (APP) is thought to play a key role in the

pathogenesis of Alzheimer's disease. Genetic studies have shown that mutations in APP, as well as genes involved in APP processing are implicated in disease development. It is possible that drugs which inhibit A aggregation may therefore be useful in its treatment. In the present study, Gestwicki and colleagues developed a novel approach. They envisioned a Trojan Horse strategy in which a small bifunctional molecule would gain access to the relevant biologic compartment and bind tightly to a chaperone, and thereby, gain steric bulk needed to disrupt a protein-protein interaction. To test this hypothesis Gestwicki et al synthesized small molecules that increased their steric bulk by binding to chaperones, but also had a moiety available for interaction with A. The entity which they utilized to bind A was Congo Red, and the compound which they used to bind to a chaperone was an enzyme inhibitor, FK506, which binds to the FKBP chaperone family. They developed a large number of compounds, these compounds showed a markedly increased potency in their ability to block -amyloid aggregation. They were effective at 50 nM, as opposed to other compounds which require a 10 nM range. They then showed that these compounds were effective in blocking toxicity to cell lines in vitro.

**COMMENTARY**

This finding raises the possibility that it may be possible to develop new small molecule inhibitors of A aggregation. This might be a novel therapeutic approach for the treatment of Alzheimer's disease. The one caveat is they have not yet shown that these compounds are going to be effective in animal studies. — **M. FLINT BEAL**

# Intermediate Filament Diseases

ABSTRACT & COMMENTARY

***Synopsis:*** *Further research will be required to understand the pathogenesis of these disorders.*

**Source:** Omary MB, et al. Intermediate Filaments Proteins and Their Associated Diseases. *N Engl J Med.* 2004;351: 2087-2100.

Microfilaments, intermediate filaments, and microtubules constitute the cytoskeletal fibrillary family of proteins. Intermediate filaments (IF) are the most abundant, encoded by at least 65 functional genes. Long, rope-like, coiled coils, IF are composed of 2 alpha-helices wound around each other, 310 to 352 amino acids in length, with linker regions of 8 to 17 amino acids connecting these coils to form longer segments. Phosphorylation, glycosylation, and transglutamination are among the modifications that regulate these filaments, which also interact with linkers, bundlers, chaperones, kinases, apoptosis-related proteins, and nuclear proteins. Filament organization, solubility, susceptibility to degradation, and formation of inclusion bodies may all be modified by these factors. Functionally, they provide the scaffolding necessary for cell integrity, protect against non-mechanical stress and apoptosis, and aid axonal and dendritic extension.

Desmin related myopathy, identified in 1998 as the first non-keratin intermediate filament disease, results in distal weakness, cardiac arrhythmias, and restrictive heart failure due to accumulation of desmin aggregates in cardiac and skeletal muscle cells. Gain-of-function mutations of alphaB-crystallin, a chaperone regulating various cytoplasmic IF, also results in desmin myopathy. Emery-Dreyfuss and limb-girdle muscular dystrophy are laminopathies resulting from lamin A and C gene mutations. Both comprise muscle weakness and cardiac conduction defects with the former including elbow and heel contractures. Lamin A and C gene mutations also result in axonal neuropathy, ie, Charcot-Marie-Tooth disease type 2B1, which may be caused by neurofilament gene mutations as well. Neurofilament light chain gene mutations are involved in Types 2E and 1F Charcot-Marie-Tooth disease, while neurofilament heavy chain mutations are considered a risk factor in the development of amyotrophic lateral sclerosis, though no definitive causative association has been established. Non-neurologic disorders involving IF gene mutations include diseases of the skin and epithelium (epidermolysis bullosa simplex), hair (monilethrix, a disorder comprising alopecia and fragile hair), corneal dystrophy, dilated cardiomyopathy, and Werner's syndrome of premature aging and senescence.

Further research will be required to understand the pathogenesis of these disorders. Therapeutics remains supportive in nature, with no method available to directly address the underlying disorder. With elucidation of disease mechanisms, however, it is hoped that tailored treatments will become a reality.

## COMMENTARY

Although composed of different proteins, intermediate filaments, microfilaments, and microtubules are in constant and intimate communication, with intermediate filament proteins serving as important components in mediating this cross-talk (*Nat Rev Mol Cell Biol.* 2004;5;601-613). Five distinct types of intermediate filament proteins are recognized: types I and II (keratins), type III (vimentin, desmin, glial fibrillary acidic protein, and peripherin), type IV (3 neurofilament subunits, NF-L, NF-M, and NF-H, nestin, syncoilin, and alpha-internexin), and type V (lamin A, its splice variant lamin C, lamin B1, and lamin B2). Extending radially from the nucleus through the cytoplasm and to the cell surface, intermediate filaments are ideally positioned to coordinate cytoskeletal cross-talk. Microtubule- and microfilament-based motility are crucial for the assembly and maintenance of this scaffolding, which in turn are regulated by intermediate filament phosphorylation and microtubule-associated proteins, including tau.

Functionally, intermediate filaments are differentially expressed at various stages of nerve cell development and regeneration, and their cytoskeletal crosstalk may be central to the determination and maintenance of the diverse cell shapes seen during these periods. Cell movement and cell division may similarly be controlled by intermediate filaments, given their role involving signaling pathways which regulate microtubule and microfilament function and organization. — **MICHAEL RUBIN**

# TBI: CRASH Kills Corticosteroids

ABSTRACT & COMMENTARY

***Synopsis:*** *There is an increase in mortality with methylprednisolone in the 2 weeks after head injury. The cause of the rise in risk of death within 2 weeks is unclear.*

**Source:** Roberts I, et al. Effect of Intravenous Corticosteroids on Death Within 14 Days in 10,008 Adults With Clinically Significant Head Injury (MRC CRASH Trial): Randomized, Placebo-Controlled Trial. *Lancet*. 2004;364:1321-1328.

TRAUMATIC BRAIN INJURY (TBI) ACCOUNTS FOR about 52,000 deaths yearly in the United States, and several million worldwide. Motor vehicle accidents are the major cause of TBI in young people; falls are the leading cause of death and disability in the elderly.

The most serious consequence of TBI is elevation of intracranial pressure (ICP), leading to lethal brain herniation. For the last 30 years, corticosteroids have been used to control elevated ICP in TBI patients. In 1997, a systematic review of published trial data suggested that the absolute risk of death in corticosteroid-treated patients was only about 1-2% lower than in controls. In 1998, the CRASH trial (Corticosteroid Randomization After Significant Head injury) was initiated to confirm or deny the effectiveness of corticosteroids in TBI.

The CRASH trial was a large, international, randomized, placebo-controlled trial of the effect of early administration of methylprednisolone on risk of death within 2 weeks and disability at 6 months after TBI. Adults with TBI were screened for inclusion within 8 hours of injury. Patients with a Glasgow Coma Scale (GCS) score of 14 or less, who were eligible for the study, were randomized to receive an intravenous infusion either of methylprednisolone (2g over 1 hour followed by a maintenance dose of 0.4g per hour) or of placebo for 48 hours.

Mortality data were collected at death, discharge, or at 2 weeks. Disability was assessed at 6 months, by a questionnaire that was mailed to patients or their caregivers, by telephone interview, or during a face-to-face interview.

The CRASH trial was powered to show a 2% difference in survival on an intention-to-treat basis, and Roberts and colleagues planned to enroll 20,000 patients. After 10,008 patients had been randomized, the data monitoring committee disclosed the unmasked results to the trial steering committee, which then stopped recruitment. The results were an unpleasant surprise: 21% of 4985 treated patients died within 2 weeks of randomization, compared with 18% of 4979 placebo patients. The relative risk of death from all causes in patients allocated to corticosteroids, compared with the placebo group, was 1.18 (95%, CI 1/09-1/27; $P = 0.0001$). The relative risk of death did not differ by severity of injury ($P = 0.22$) or time since injury ($P = 0.05$). There was no observed increase in complications with corticosteroid use. The effect of corticosteroids on disability at 6 months will be reported later.

## COMMENTARY

The CRASH trial results show that corticosteroids should not be used to treat head injury, whatever the severity. In editorial comments, Saverland and Maegele[2] point out that the CRASH trial

left the unanswered, critical question of why corticosteroids significantly increased mortality. Therefore, clinicians are left to wonder how corticosteroids harmed TBI patients. The results of the CRASH trial will also raise doubts about the effectiveness of corticosteroid therapy in patients with traumatic spinal cord injury, where their use is well established. A recent critical review questioned the validity of existing trials of methylprednisolone in acute spinal cord injury.[3]

Roberts et al deserve our thanks and admiration for having completed one of the largest clinical trials in emergency patients with impaired consciousness. They have provided a definitive answer to an important therapeutic question. The use of corticosteroids in TBI now joins an ever-lengthening list of treatments that once were in widespread clinical use, but whose effectiveness could not be shown in large-scale, randomized trials. Goodbye to corticosteroid in TBI. — **IGOR OUGORETS AND JOHN J. CARONNA**

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2. Saverland S, et al. *Lancet.* 2004;364:1291-1292.
3. Coleman WP, et al. *J. Spinal Disord.* 2000;13:185-199.


## Sensory Polyradiculopathy

ABSTRACT & COMMENTARY


***Synopsis:*** *This condition preferentially affects large myelinated fibers of the posterior roots, may respond favorably to treatment, and may be a restricted form of chronic inflammatory demyelinating polyradiculoneuropathy.*



**Source:** Sinnreich M, et al. Chronic Immune Sensory Polyradiculopathy: A Possibly Treatable Sensory Ataxia. *Neurology.* 2004;63;1662-1669.


Retrospective chart review from 1990-2002 at the Mayo Clinic revealed 15 patients with sensory ataxia due to inflammatory demyelination at the dorsal root level. Criteria for including patients in the analysis comprised a sensory syndrome in the absence of muscle weakness, normal peripheral nerve conduction study and electromyography with abnormal somatosensory evoked potentials, and neuroimaging studies of the neuraxis that excluded a compressive lesion, but were consistent with nerve root inflammation. Nerve rootlet biopsy data was available in 3 patients. All had normal or negative B12 levels, syphilis serology, thyroid function, ACE level, and ANA and ENA antibodies. Paraneoplastic antibody screen was negative in all 12 patients tested.

Among the 15 patients, 10 men and 5 women with a median age of onset of 63 years, all experienced gait ataxia, causing frequent falls in 9; 3 required wheelchair assistance. Arm ataxia was present in 7. Leg paresthesiae and dead-like numbness was experienced in all patients, with arm paresthesiae and numbness in 12 and 4, respectively. Onset was unilateral or asymmetric in 7, progressed in all with no instance of spontaneous improvement, and eventually became symmetric in 12. Examination revealed impaired position and vibration sensation in all, with absent deep tendon reflexes in 14 and impaired small fiber sensation in 10. None had weakness (by choice of inclusion criteria). Cerebrospinal fluid protein elevation was documented in 13 of 14 patients tested; values ranged from 31 to 161 mg/dL, with a median of 83 mg/dL. None demonstrated white cells or oligoclonal bands. Enlarged lumbar nerve roots were seen on MRI in 5; 3 showed enhancement with GAD. Sural nerve biopsy was normal in 2. Nerve rootlet biopsy in 3 showed decreased numbers of large myelinated fibers, with onion bulb formation and demyelinated axons in 2. Intravenous immunoglobulin alone (n = 4) or combined with intravenous steroids (n = 2) administered to the 6 most severely affected patients, resulted in striking improvement in all; 4 returned to independent ambulation. Chronic inflammatory sensory polyradiculopathy (CISP) appears to be an autoimmune mediated syndrome affecting the dorsal roots proximal to the dorsal root ganglia, and is responsive to immune modulating therapy. It is eminently treatable, and should not be overlooked.

### COMMENTARY

Chronic inflammatory sensory polyradiculopathy may have a motor equivalent. One month following a low grade fever and upper respiratory tract infection, and 12 days following maintenance chemotherapy including intrathecal methotrexate, Ara-C, and hydrocortisone, with intravenous vincristine, for acute lymphocytic leukemia (ALL) in remission, bilateral leg weakness, and areflexia developed in a 3-year-old girl (*Muscle Nerve.* 2002;25;106-110). Sensation was normal, as were blood studies including complete blood count, ery-

throcyte sedimentation rate, creatine kinase, thyroid-stimulating hormone, and blood cultures. Cerebrospinal fluid analysis showed no malignant cells or white cells, but elevated protein (107mg/dL). Lumbar MRI with GAD revealed enhancement of multiple ventral nerve roots of the cauda equina. Initial electrodiagnostic studies revealed normal sensory nerve conduction studies, low motor evoked amplitudes, absence of motor conduction block, and no spontaneous activity on needle electromyography. Empirical treatment with intravenous immunoglobulin resulted in improvement within 3 days, and independent ambulation with return of reflexes by 4 weeks. CSF remained free of malignant cells, and later needle EMG showed denervation and reinnervation. This patient's clinical presentation, electrodiagnostic studies, CSF protein, MRI, and response to intravenous immunoglobulin are consistent with an autoimmune process affecting the ventral roots triggered by her antecedent URI or chemotherapy or both, and may be the motor equivalent of chronic inflammatory sensory polyradiculopathy. — **MICHAEL RUBIN**

# A New Genetic Defect in Charcot-Marie-Tooth Disease Links It to Mitochondrial Dysfunction

ABSTRACT & COMMENTARY

***Synopsis:*** *The present findings raise the possibility that new effective therapies may be developed for CMT2A, which target the underlying pathophysiology.*

**Source:** Zuchner S, et al. Mutations in the Mitochondrial GTPase Mitofusin 2 Cause Charcot-Marie-Tooth Neuropathy Type 2A. *Nat Genet.* 2004,36:449-451.

CHARCOT-MARIE-TOOTH DISEASE (CMT) IS AN inherited peripheral neuropathy which leads to characteristic features of peroneal atrophy, weakness pes cavus, and sensory loss. Symptoms often begin in the first or second decade of life. However, in some cases, they can occur much later According to electrophysiological criteria, CMT falls into 2 main categories. The first is the demyelinating CMT type 1. This is associated with decreased nerve conduction velocities. It has been shown to be due to a duplication of the human peripheral myelin protein 22, which results in 3 copies of the gene. This duplication is found in 70-85% of both autosomal dominant and isolated CMT-1 cases.

The second major category of CMT is type 2, or the axonal form. There are a number of subcategories of CMT type 2. It manifests either normal or minimally reduced nerve conduction velocities. A mutation in the gene KIF1B was previously reported in 1 Japanese family with CMT2A. No further mutations in this gene, however, have been identified by linkage studies in a large number of families with CMT2A.

In the present report, 7 families with CMT2A were defined with the classical phenotype, and in different ethnic backgrounds. It was found by direct sequencing and lod scores that the primary gene mutated was the mitochondrial fusion protein mitofusin 2 (MFN2). This was shown to be caused by a number of point mutations in this gene. A large number of other genes were excluded, including KIF1B. MFN2 is localized to the outer mitochondrial membrane, where it regulates the mitochondrial network architecture by fusion of mitochondria. All the mutations which were identified, co-segregated with the disease phenotype in the respective families. The mutations were in regions which are highly conserved across numerous species.

Mitochondria normally undergo a dynamically-regulated balance between fusion and fission reactions. It is likely that disruption of this network will lead to impaired mitochondrial function. It is known that mitochondria need to be moved up and down the axons in order to replenish their proteins and acquire nuclear proteins in the perinuclear region. It has been demonstrated that MFN2 knockout mice have a lethal phenotype. A virally transported MFN2 construct however, rescues the MFN2 deficient mouse cell line. This restores a normal phenotype. It corrects the fusion fission imbalance, which suggests the possibility that CMT2A may be amenable to some type of gene therapy in the future.

## COMMENTARY

The present findings are the first to link a defect in the nuclear encoded mitochondrial gene to a peripheral neuropathy. Previous studies have shown that defects in mitochondrial DNA, such as the T8993G mutation, result in the syndrome of NARP, which consists of neuropathy, ataxia, and retinitis pigmentosa. Cell lines with this mutation show defects in oxidative phosphorylation that can be corrected by antioxidants. This raises the possibility that antioxi-

dants might also show some benefits for patients with CMT2A. The present findings raise the possibility that new effective therapies may be developed for CMT2A, which target the underlying pathophysiology. — **M. FLINT BEAL**

## CME Questions

1. **Intermediate filaments include:**
   a. keratins.
   b. vimentin, desmin, glial fibrillary acidic protein, and peripherin.
   c. neurofilament subunits, nestin, syncoilin, and alpha-internexin.
   d. lamin A, lamin C, lamin B1 and lamin B2.
   e. All the above

2. **In the CRASH trial, the risk of death after TBI in the corticosteroid group compared with the control group was:**
   a. 1% less (than controls).
   b. equal.
   c. 1% more.
   d. 2% more.
   e. 3% more.

3. **Chronic inflammatory sensory polyradiculopathy appears to be:**
   a. an autoimmune mediated syndrome affecting the dorsal roots.
   b. responsive to immune modulating therapy.
   c. associated with normal peripheral nerve conduction study and electromyography.
   d. associated with abnormal somatosensory evoked potentials.
   e. All the above

**Answers:** 1. (e); 2. (e); 3. (e)

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**In Future Issues:**

**The EEG in CJD**

PHARMACOLOGY WATCH

# Hypertension: Therapy vs Calcium Channel Antagonists

Pharmacotherapy of hypertension has been much in the news in the last 2 months. Standard therapies such as atenolol have been challenged, while calcium channel antagonists may be making a comeback.

Researchers from Sweden performed a meta-analysis of 9 randomized, controlled trials that looked at the effectiveness of atenolol on cardiovascular morbidity and mortality in patients with hypertension. Four of the studies compared atenolol with placebo or no treatment, and 5 studies compared atenolol with other antihypertensive drugs. Although atenolol was effective at lowering blood pressure, there were no outcome differences with regard to all cause mortality (RR 1.01; 95% CI, 0.89-1.15), cardiovascular mortality (RR 0.99; 95% CI, 0.83-1.18), or myocardial infarction (RR 0.99; 95% CI, 0.83-1.19), compared to placebo. The risk for stroke was lower with atenolol, compared to placebo (RR 0.85; 95% CI, 0.72-1.01). When compared with other antihypertensives, no difference in blood pressure lowering was noted between treatment groups, but the meta-analysis revealed a higher mortality with atenolol, compared with other treatments (RR 1.13; 95% CI, 1.02-1.25). This included a higher risk of cardiovascular mortality and stroke. The authors suggest that the results "cast doubts on atenolol as a suitable drug for hypertensive patients." They further postulate that atenolol's low lipophilic profile, which theoretically may reduce its ability to prevent cardiac arrhythmias, could be responsible for these findings (*Lancet.* 2004; 364: 1684-1689). Some have criticized the study because it did not include newer well-designed trials in which atenolol was used in combination with other drugs including diuretics. In these studies, including ALLHAT and SHEP, the addition of atenolol resulted in overwhelming benefit. In the meantime, use of atenolol as monotherapy needs to be reevaluated, however, addition of atenolol to an existing regimen will probably remain a part of most clinical guidelines.

### *GEMINI Trial*

Speaking of beta-blockers, a new study suggests that carvedilol may be a better choice for diabetic patients than metoprolol. The Glycemic Effects in Diabetes Mellitus: Carvedilol-Metoprolol Comparison in Hypertensives (GEMINI) trial was designed to compare the effects of beta-blockers with different pharmacological profiles on glycemic and metabolic control in diabetic patients who were already receiving renin-angiotensin system (RAS) blockade with either a ACEI or ARB. Over 1200 patients with diabetes and hypertension were randomized in GEMINI. The main outcome was change in baseline HbA1c after 5 months of therapy. A difference was noted in mean change of HbA1c for baseline between the drugs (0.13%;95%CI -0.22%-0.4%. *P*=.004) The mean HbA1c increased with metoprolol (0.15% [0.04%]; *P* < .001), but not for carvedilol (0.02% [0 .04%]; *P* =

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.65). Insulin sensitivity also improved with carvedilol but not with metoprolol, and progression to microalbuminuria was less frequent carvedilol than with metoprolol (6.4% vs 10.3%; *P* = .04). The drugs were used in equipotent doses to achieve similar blood pressure lowering effects. The authors conclude that the carvedilol, used in the presence of RAS blockade, does not effect glycemic control, and improves some components of metabolic syndrome relative to metoprolol in patients with diabetes and hypertension (*JAMA.* 2004;292:2227-2236). The study points out again that beta-blockers, with variable pharmacologic effects, may result in different clinical outcomes. Carvedilol is a nonselective beta antagonist, but has alpha 1 antagonist properties and mild vasodilatory properties.

## CAMELOT Trial

The calcium channel antagonist amlodipine has beneficial cardiovascular effects in heart patients even if they have normal blood pressure according to new study. The Comparison of Amlodipine vs Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study compared amlodipine 10 mg, enalapril 20 mg or placebo in patients with documented CAD and diatolic blood pressures < 100 mm Hg. The outcome measures were incidence of cardiovascular events and a second outcome was the use of intravascular ultrasound to measure atheroma volume. Nearly 2000 patients were followed over 24 months. New cardiovascular events (cardiovascular deaths, non-fatal myocardial infarction, resuscitated cardiac arrest, coronary revascularization, hospitalization for angina actors, hospitalization for congestive heart failure, fatal or non-fatal stroke or transient ischemic attack, or new diagnoses of peripheral vascular disease) occurred in 23.1% of placebo treated patients, 16.6% of amlodipine treated patients (HR 0.69; 95% CI, 0.54-0.88 [*P* = .003]) and 20.2% of enalapril treated patients (HR, 0.85; 95% CI, 0.67-1.07 [*P* = .16]). Plaque volume by ultrasound showed a trend towards less progression of atherosclerosis in the amlodipine group vs placebo (*P* = .12), with significantly less progression in the subgroup of patients with higher systolic blood pressures (*P* = .02). Compared with baseline atheroma volume progression in the placebo group (*P* < .001), the study showed a trend towards progression in the enalapril group, and no progression in the amlodipine group. The authors conclude that amlodipine reduced cardiovascular events and slowed progression of atherosclerosis in patients with CAD and normal blood pressure (*JAMA.* 2004;292:2217-2225). An accompanying editorial reviews the data and suggests mechanisms for the findings. More than any other factor, the editorialists suggest that lowering blood pressure to a systolic in the 120 mm Hg range may be the most important factor of all in patients with CAD (*JAMA.* 2004;292:2271-2273).

## INVEST Trial

The INVEST study suggests that verapamil is as effective as atenolol with regard to benefit and side effects in diabetic patients with hypertension (*Hypertension* 2004;44:614-615). The PEACE trial looked at patients with coronary disease and normal or slightly reduced left ventricular function to assess whether addition of an ACE inhibitor would convey benefit, and found no benefit for these patients (*N Engl J Med.* 2004; 351:2058-2068).

## The Dangers of Vitamin E

And vitamin E? Don't expect it to prevent cardiovascular disease or cancer for that matter. As vitamin E doses increase, so does all cause mortality, according to a large meta-analysis. Nineteen trials, which included nearly 136,000 participants, were evaluated in the analysis, of which 11 tested high dose vitamin E (400 IU/d). The pooled all-cause mortality risk difference for the high-dosage vitamin E was 39 per 10,000 (95% CI, 3-74 per 10,000; *P* = .035). For doses less than 400 IU/d, the mortality risk difference was 16 per 10,000 (CI, -41 to 10 per 10,000; *P* > .2). A dose-response analysis revealed an increase in all cause mortality with vitamin E dosages > 150 IU/d. The authors suggest that an increased mortality with higher doses of vitamin E is biologically plausible. Low doses of vitamin E may have some antioxidant effects, but higher doses may be pro-oxidant, particularly to LDL cholesterol. High doses of vitamin E may also displace other fats soluble antioxidants, disrupting the natural balance of antioxidant systems. Vitamin E may also be a mild anticoagulant, which may explain the increased hemorrhagic stroke seen in some vitamin E trials. This study was felt important enough to warrant early release online, since many people worldwide take vitamin E supplements on a daily basis far in excess of 400 IU/d. The full study will be published in the January 2005 *Annals of Internal Medicine*.

## FDA Actions

The FDA has approved a new biologic for the treatment of relapsing forms of multiple sclerosis. Natalizumab is a monoclonal antibody that is given intravenously once a month. It will be marketed by Biogen as Tysabi.