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Promising Novel Therapy for Multiple Sclerosis

ABSTRACT & COMMENTARY

Source: Miller DH, et al. A controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2003;348:15-23.

NATALIZUMAB (ANTEGREN) IS A HUMANIZED MONOCLONAL antibody against an alpha-4 integrin expressed on activated lymphocytes, which is required for adhesion to the vascular endothelium and penetration into the nervous system. In this randomized, double-blind trial, a total of 213 patients with relapsing-remitting or relapsing secondary progressive multiple sclerosis were assigned to 1 of 3 groups: natalizumab at 3 or 6 mg/kg (68 and 74 patients, respectively), or placebo (71 patients), by infusion every month for 6 months. The primary end point was the number of new gad-enhancing brain lesions on monthly MRIs. Clinical outcomes of relapse rate and self-reported well-being were also measured. There were marked reductions in the mean number of gad-enhancing lesions in both treated groups: 0.7 and 1.1 new lesions in the 3 and 6 mg/kg groups, respectively, compared with 9.6 lesions in the placebo group ($P < .001$). There were corresponding reductions in clinical relapses: 13 and 14 attacks in the 3 and 6 mg/kg groups, compared with 27 attacks in the placebo group ($P = .02$). The patients also subjectively felt better in the treated groups.

COMMENTARY

An early step in the destructive inflammatory pathology in multiple sclerosis is the attachment of activated lymphocytes and monocytes to the vascular endothelium and subsequent entry into the brain parenchyma. Hence, the selective blockade of adhesion molecules by monoclonal antibody technology, to limit cell penetration into the central nervous system, would appear to be a logical therapeutic strategy. The above study demonstrates by convincing MRI and clinical measures the ability of natalizumab to significantly reduce disease activity in multiple sclerosis. These findings will need to be confirmed in larger trials of longer duration, which are currently under way. — **BRIAN R. APATOFF**

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INSIDE

Late Secondary Injury May Limit the Effectiveness of Thrombolysis

ABSTRACTS & COMMENTARY

Sources: Kidwell CS, et al. Late secondary ischemic injury in patients receiving intraarterial thrombolysis. *Ann Neurol*. 2002;52:698-703; Fisher M. Editorial. Reversal of diffusion abnormalities after ischemic stroke: Adding difficulty and complexity to the conundrum of acute stroke imaging. *Ann Neurol*. 2002;52:695-696.

WITHIN MINUTES OF AN ACUTE CEREBRAL ISCHEMIC insult, diffusion-weighted magnetic resonance imaging (DWI) demonstrates ischemic regions with a decline in the apparent diffusion coefficient (ADC) of water.[1] ADC decline is associated with impaired high-energy metabolism and loss of ion homeostasis. Animal studies and preliminary observations in humans demonstrate that initial DWI and ADC abnormalities are reversible by early reperfusion.[2] Additional animal studies indicate that ischemic tissue that undergoes early reversal of DWI abnormalities may manifest either sustained reversal and tissue salvage or only temporary reversal followed by later reappearance of DWI abnormalities, indicating late, secondary injury.[3,4]

Kidwell and associates studied the phenomenon of late secondary ischemic injury in 18 ischemic stroke patients treated within 6 hours of stroke onset with intraarterial thrombolysis alone (n = 12) or a combination of intravenous and intraarterial thrombolysis (n = 6). Ten patients (56%) demonstrated no reversal in the size of the DWI lesion after treatment. Eight of 18 patients (44%) demonstrated some amount of ADC reversal when DWI was repeated several hours after thrombolysis. At day 7, however, MRI showed that 5 of 8 patients (28%) had partial or complete reappearance of a DWI abnormality that initially had resolved. Three of 8 (17%) had no secondary ADC changes.

There was no significant difference among these 3 groups in age, time to recanalization, time to post-treatment MRI, degree of vessel recanalization, or occurrence of post-ischemic hyperperfusion. None of the patients showing late secondary injury had evidence of vessel reocclusion on perfusion MRI, MRA, or transcranial Doppler examination. Pretreatment ADC values, however, were lowest in tissues without reversal, intermediate in tissues with late injury, and highest in tissues with sustained reversal. This finding suggests that a profound degree of initial ischemia leads to irreversible infarction, intermediate degrees of ischemia permit initial normalization of DWI abnormalities but promote late secondary injury, and modest degrees of ischemia allow sustained reversal of abnormalities and tissue survival.

Clinically, although patients with sustained reversal of DWI abnormalities showed greater improvement in their median NIH stroke scale scores than did patients with no reversal, the difference was not statistically significant.

COMMENTARY

The clinical significance of late secondary injury remains uncertain. Nevertheless, the present study suggests that late secondary injury occurs with intermediate durations of ischemia and can compromise some or all of the initially salvaged brain tissue. Therefore, Kidwell et al have set the stage for additional investigations to determine the mechanisms, frequency, temporal and spatial evolution, and the clinical significance of late secondary injury. Once the mechanism of injury has been determined, neuroprotective agents can be developed that specifically target late secondary injury.

For the present, the suggestion that delayed tissue injury may limit neurological recovery after successful thrombolysis provides a rationale for further stroke treat-

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ment trials of combination thrombolytic and neuroprotective treatment strategies. — **JOHN J. CARONNA**

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Blood Pressure Treatment for Stroke Patients: What Should Be the First Line?

ABSTRACT & COMMENTARY

Source: Major outcomes in high-risk hypertensive patients randomized to angiotensin converting enzyme inhibitor or calcium channel blocker vs. diuretic. The antihypertensive and lipid lowering treatment to prevent heart attack trial (ALLHAT). *JAMA*. 2002;288:2981-2997.

THE PUBLICATION OF THE ALLHAT TRIAL RECEIVED much publicity not only in medical circles but was also front-page news in the *Wall Street Journal*. This trial was a significant blow to the pharmaceutical industry, and it convincingly showed that inexpensive diuretic medications had superiority over highly marketed ACE inhibitors and calcium channel blockers for the treatment of hypertension.

ALLHAT included more than 33,000 participants with hypertension and 1 other vascular problem such as prior myocardial infarction or stroke, diabetes, smoking, and hyperlipidemia. Subjects, not previously treated for their blood pressure, were randomly assigned to a regimen of diuretic (chlorthalidone), ACE inhibitor (lisinopril), or calcium channel blocker (amlodipine). Additional drugs such as atenolol were added in an open-label format. There were no differences between the 3 treatment regimens in the primary outcome measure of fatal or nonfatal MI. Perhaps more importantly, chlorthalidone was about 20% superior to lisinopril in preventing stroke; it was a stronger antihypertensive and even appeared to produce less congestive heart failure than lisinopril, a disorder thought optimally treated with ACE inhibition. Chlorthalidone was also superior to lisinopril when all vascular disorders (MI, stroke, and peripheral vascular disease) were lumped together.

COMMENTARY

How should neurologists interpret these results? Within the past 2 years there have been important reports in the stroke literature suggesting that ACE inhibitors should be considered a crucial part of any drug cocktail for the "post-stroke" patient. Both the Perindopril Protection Against Recurrent Stroke Study (PROGRESS) and Heart Outcomes Prevention Evaluation (HOPE) trial suggested that ACE inhibition provided about a 30% relative risk reduction of recurrent stroke independent of any effects on blood pressure. How should these trials now be viewed? Interestingly, the PROGRESS study, largely heralded as an ACE inhibitor trial, also included the diuretic indapamide. Deeper analysis of PROGRESS indicates that a large portion of benefit ascribed to the treatment regimen may have been explained by the inclusion of indapamide. While patients treated with the combination of perindopril and indapamide had reduced stroke risk over placebo patients, those treated only with perindopril had minimal blood pressure reductions and no significant decrease in stroke.

ALLHAT was a nearly flawless study methodologically, but it is nevertheless open to deeper analysis as well. Nearly one-third of the ALLHAT participants were black, an overall plus, reflecting an ethnically diverse patient pool. It is well known, however, that hypertension in blacks is caused by a hyper-reninemic state and that this pathophysiology is optimally treated with diuresis. Indeed, in subgroup analysis, blacks in ALLHAT on ACE inhibitors had suboptimally controlled blood pressures and higher incidences of stroke/MI. In contrast, the relative risk of stroke for whites on ACE inhibitors compared to diuretic was 1.00, reflecting overall clinical equivalence. Physicians treating primarily white populations may need to take these differences into account.

Much of the publicity surrounding ALLHAT was financial, critical of trends toward more expensive drugs driven by pharmaceutical detail men. The cost issues, however, are not cut and dry. Diuretics are inexpensive, but there are also off-patent ACE inhibitors available such as captopril, enalapril, and lisinopril. Angiotensin receptor blockers are expensive and should only be used when standard ACE inhibitors cannot be tolerated.

In conclusion, ACE inhibitors and diuretics are both appropriate first-line blood pressure therapies for stroke patients. Ultimately, since many of our patients require combination therapy with both of these drugs, head-to-head comparisons may be less important than an emphasis on continued careful diligence to strict blood pressure control. — **ALAN Z. SEGAL**

Do Statin Drugs Prevent Dementia? Data from the PROSPER Study

ABSTRACT & COMMENTARY

Source: Shepherd J, et al. Pravastatin in elderly individuals at risk of vascular disease (PROSPER): A randomized controlled trial. *Lancet*. 2002;360:1623-1630.

Among patients with coronary artery disease, HMG CoA reductase inhibitors (statins) are a mainstay of therapy. These drugs have also become widely prescribed with a low threshold to patients with elevated cholesterol and even minimal cardiac risk factors. The role of statins in patients with stroke and other forms of neurological disease is less well defined. Because statins inhibit the activity of beta and gamma secretases, enzymes involved with the cleavage of amyloid precursor protein, they are now thought to be potentially efficacious in preventing the formation of amyloid plaques and the onset of clinical Alzheimer's disease (AD). Cholesterol lowering may further protect against dementia by limiting the damaging effects of apolipoprotein E, specifically in those patients with the APO e4 allele, a known risk factor for AD. Statins may furthermore be beneficial in the prevention of "vascular" or "multi-infarct" dementia by preventing small vessel strokes or by endothelial remodeling on a microvascular level.

In the pravastatin in elderly individuals at risk of vascular disease (PROSPER) study, 5804 individuals aged 70-82 were randomized to pravastatin 40 mg/d or placebo. Subjects either had a history of vascular disease or had vascular risk factors. The primary outcome measure was a composite end point of coronary death, nonfatal myocardial infarction, or stroke, measured after 3 years of therapy. Pravastatin reduced LDL cholesterol by 34%, from a mean of 146 mg/dL to approximately 100 mg/dL. Statin therapy reduced the risk of a primary end point by 15%. In subgroup analysis, coronary events were reduced by 19%, while no discernable effect was found for stroke. Transient ischemic attack was reduced by 25% but was of borderline significance. The overall incidence of stroke outcomes was low, occurring in 116 treated patients and 119 in the placebo group.

Cognitive outcomes were studied by multiple measures, including digit span, picture-word recall, Stroop test, and mini-mental status examination. Functional outcomes were also explored, including the Barthel index and the instrumental activities of daily living score. Statin therapy had no significant effect on any of these outcomes.

COMMENTARY

The results of the PROSPER study are taken in the context of those of the larger British Heart Protection Study (HPS), which was also reported in *Lancet* this year.[1] Unlike PROSPER, the HPS study did show a decrease in stroke risk. HPS followed patients for a longer period of time (5 years) and had more cerebrovascular outcomes, 444 treated vs 585 placebo (P = 0.002). These differences, however, did not impact cognitive decline. As in PROSPER, statin therapy (in the case of HPS-simvastatin) did not prevent dementia. Although pravastatin and simvastatin are quite similar, it is intriguing that the latter is a possibly more efficacious cerebrovascular drug since it is more lipophilic and may have greater CNS penetration.

These data provide further support to the concept that statin therapy should be prescribed to prevent coronary events in patients with known disease or with risk factors, regardless of age. Both PROSPER and HPS indicate that older age patients (older than 70) derive similar cardiac benefits to younger patients.

These data are less clear about the prevention of stroke and dementia. Part of this problem lies in the heterogeneity of the dementing disorders. Do statins prevent vascular dementia through the prevention of small vessel strokes and microvascular disease? Or do they prevent AD through effects on amyloid? Do other forms of dementia such as Diffuse Lewy Body Disease factor into this equation in any important way?

In addition to their high cost, statins are not free of side effects. Particularly when taking atorvastatin, patients develop often-disabling myalgias, even with normal measurements of CPK. Perhaps as more elderly individuals are treated with statins we may be able to glean information from observational studies. There does not seem justification to begin widespread prophylactic use at this time. **— ALAN Z. SEGAL**

Reference

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IVIG for MG

ABSTRACT & COMMENTARY

Source: Wegner B, Ahmed I. Intravenous immunoglobulin monotherapy in long-term treatment of myasthenia gravis. *Clin Neurol Neurosurg*. 2002;105:3-8.

Intravenous immunoglobulin (IVIG) is safe and effective therapy for acute exacerbations of myasthe-

nia gravis (MG), myasthenic crisis, and for optimizing patients' conditions in preparation for thymectomy. Its role in the long-term management of MG remains to be defined. Six patients with seropositive MG of 6 months to 10 years duration had been treated with a combination of Mestinon (n = 6), steroids (n = 4), plasmapheresis (n = 2), or thymectomy (n = 3). Intolerable side effects mandated a change in therapeutic regimen. All received IVIG infusion of 400 mg/kg/d for 5 days followed by IVIG 400 mg/kg/d for 1 or 2 days every 2 or 3 months. Follow-up extended for 24-36 months. All patients were successfully weaned off all MG medication, including Mestinon and prednisone, without worsening of their Osserman classification scores. No complications were experienced. Bi- or tri-monthly IVIG infusion, for merely a day or 2, can be a useful therapeutic alternative in the management of seropositive myasthenic patients.

COMMENTARY

What about myasthenics who are acetylcholine receptor (AchR) antibody-negative? Upward of 20% of myasthenics are so-called seronegative. Nevertheless, they respond to plasmapheresis and immunosuppression, and their serum IgG causes neuromuscular transmission failure in mice. What is their target antigen? Muscle specific tyrosine kinase (MuSK) antibodies were found in 17 of 24 seronegative myasthenic patients,[1] suggesting that the target may be MuSK, an integral part of the agrin receptor at the neuromuscular junction (NMJ).

How does this fit in, so to speak, with NMJ physiology? Development of the NMJ is complex, involving both anterograde (nerve to muscle) and retrograde (muscle to nerve) signals. Agrin, a nerve-derived signal, induces clustering of AchR on myotube surfaces at a density equivalent to that at the mature NMJ (12,000/mm^2) suggesting that it is involved in the development of the post-synaptic complex.[2] It is a member of the heparan sulfate proteoglycan family and is a multidomain protein, containing regions of homology with laminin (cell adhesion protein) and epidermal growth factor. It exists in several isoforms and is present in brain and spinal cord, as well as muscle, liver, kidney, and lung. MuSK is a single transmembrane polypeptide, and evidence suggests that it forms at least part of the agrin receptor at the NMJ.

IgG from seronegative patients inhibits agrin-induced AchR clustering, offering a mechanism for NMJ failure in these patients. Indeed, patients negative for both AchR and MuSK antibodies also appear to have activity in their non-IgG serum fraction, which inhibits AchR function, as reported in 8 of 12 such patients.[3] AchR phosphorylation with consequent AchR dysfunction may be the pathophysiologic mechanism in these myasthenics.[3] Elucidation of the precise target in such patients will improve understanding of NMJ physiology, as well as improve diagnosis in seronegative patients.

Similar antibody phenomenology is seen in Lambert Eaton myasthenic syndrome (LEMS) in which 85% of patients demonstrate antibodies to P/Q type voltage gated calcium channels, while 15% are seronegative. When purified IgG obtained from "seronegative" LEMS serum was injected into mice, quantal contents of the end plate potentials decreased, as they did following seropositive serum injection. Controls showed no change.[4] Seronegative LEMS, like seronegative MG, appears to be antibody mediated. Identification of the antibody and antigen in these patients is the next step in understanding their etiopathogenesis. — **MICHAEL RUBIN**

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Homocysteine and Dementia

ABSTRACTS & COMMENTARY

Sources: den Heijer T, et al. Homocysteine and brain atrophy on MRI of non-demented elderly. *Brain*. 2003;126:170-175; Kado DM, et al. Homocysteine levels and decline in physical function: MacArthur studies of successful aging. *Am J Med*. 2002;113:537-542; Dufouil C, et al. Homocysteine, white matter hyperintensities, and cognition in healthy elderly people. *Ann Neurol* (forthcoming article). Available online at http://www.interscience.com.

THREE RECENT STUDIES HAVE PROVIDED FURTHER evidence linking elevated homocysteine levels to brain atrophy and cognitive dysfunction, as well as a decline in physical function. The first of these studied whether higher homocysteine levels are involved in the early pathogenesis of Alzheimer's disease. den Heijer and colleagues measured hippocampal, amygdala, and global brain atrophy on brain MRI. The study was part of the Rotterdam study, which is a large population-based study of age-related brain changes. In 1077 non-demented people, aged 60-90, den Heijer et al obtained nonfasting plasma homocysteine levels in 1031 of the participants and in 505 of the participants with hippocampal and amygdalar volumes. There was a linear

relationship between higher plasma homocysteine levels and cortical atrophy per standard deviation increase. Similarly, there was more hippocampal atrophy, yet no association was observed between plasma homocysteine levels and amygdalar atrophy.

In the second study, Kado and associates performed a prospective cohort study of 499 highly functioning men and women aged 70-79 who had been enrolled in the MacArthur studies of successful aging. They measured total homocysteine levels and performance of physical function at baseline and then repeated these measures 28 months later. A summary measure of physical performance was obtained from tests of balance, gait, lower body strength and coordination, and manual dexterity. Kado et al found that with each increase and standard deviation of homocysteine there was an increased risk of being in the worst quartile of decline of physical function. This was after adjusting for other parameters such as age, sex, baseline physical performance, smoking status, vitamin B_{12} levels, and incidence of stroke. It was concluded that older persons with elevated homocysteine levels are at increased risk of decline in physical function.

The third study was part of the epidemiology of vascular aging study, which is a prospective study focusing on determinants of vascular aging and cognitive decline. Dufouil and colleagues examine the relationship between homocysteine levels and cognitive decline in 1241 subjects aged 61-73 followed up over 4 years. Dufouil et al measured plasma homocysteine levels, as well as a number of cardiovascular risk factors and ApoE genotype. Cognitive performance was assessed repeatedly using the Mini-Mental State Examination, Trail Making Test, Digit Symbol Substitution Test, and Finger Tapping Test. At 2 years of follow-up, 841 of the subjects underwent cerebral magnetic resonance imaging, and the number of white matter hyperintensities was rated visually. The major finding was that individuals who had homocysteine levels higher than 15 µmol/L showed significantly worse scores on all 4 cognitive tests. The odds of cognitive decline was 2.8-fold higher in the patients with the elevated homocysteine levels. There, however, was no relationship with numbers of white matter hyperintensities. The number of white matter hyperintensities was equal in the 4 subgroups with varying levels of homocysteine. This study has some limitations since homocysteine levels were measured only once, whereas cognitive performance was measured repeatedly. Nevertheless, none of the patients was initially demented. Also, the prospective nature of the findings are in favor of elevated homocysteine being a contributive factor to cognitive decline.

COMMENTARY

Homocystinuria is an inborn error of methionine metabolism that leads to severely elevated homocysteine levels resulting in mental retardation, lens dislocation, skeletal abnormalities, and early thrombotic events. It was subsequently hypothesized that elevated plasma homocysteine levels may be a cardiovascular risk factor in the general population. This has been confirmed in a number of studies. Of particular note, elevated homocysteine levels have been linked to carotid artery arteriosclerosis. There is a strong association of elevated plasma homocysteine and Alzheimer's disease. Studies measuring serum levels of homocysteine in patients with senile dementia of Alzheimer's type have shown significantly elevated homocysteine levels. In one study, the ratio of confirmed Alzheimer's disease associated with a total homocysteine level in the top third (greater than 14 µmol/L)compared to the bottom third (less than 11 µ mol/L) was 4.6. In the Framingham study, a total 1092 subjects without dementia were followed to establish whether elevated homocysteine levels precede the onset of dementia or result from dementia-related nutritional and vitamin deficiencies. Homocysteine levels were obtained at baseline . They were assessed for dementia 8 years later. Over the period of 8 years, dementia developed in 111 subjects, of whom 83 were given a diagnosis of Alzheimer's disease. The adjusted relative risk was 1.4 for each increase in 1 standard deviation of the homocysteine level.

In the present studies, den Heijer et al and Dufouil et al provide further evidence that homocysteine may directly contribute to developing Alzheimer's disease. They documented increased plasma homocysteine levels that were associated with more hippocampal and cortical atrophy in an older and nondemented population. The presumption is that these subjects are at risk of developing Alzheimer's disease. What is the potential mechanism of this? It has been demonstrated that homocysteine has neurotoxic effects in cortical hippocampal neuronal cultures. It also has been shown to impair DNA repair in hippocampal neurons and sensitize them to amyloid toxicity in experimental models of Alzheimer's disease. Homocysteine has also been directly linked to free radical damage. As such, the recent fortification that diet with more folate in 1996 may have major benefits in public health if it, as expected, lowers plasma homocysteine levels. In the meantime, taking folate supplements as well would make sense for high-risk individuals, particularly those with homocysteine levels greater than 15 µmol/L. — **M. FLINT BEAL**

In Epilepsy, Not All MRI Scans are Created Equal

ABSTRACT & COMMENTARY

Source: Von Oertzen J, et al. Standard magnetic resonance imaging is inadequate for patients with refractory focal epilepsy. *J Neurol Neurosurg Psychiatry*. 2002;73:643-647.

Among patients undergoing epilepsy surgery for pharmacologically refractory seizures, detection and excision of a structural lesion congruent with the electroencephalographic ictal onset is a strong predictor of a seizure-free outcome. For cases of hippocampal sclerosis (HS), the seizure-free rate can be as high as 85-90% vs a rate of about 70% for all forms of temporal lobe epilepsy. Similarly, in extratemporal cases, successful outcome from epilepsy surgery is 50% in nonlesional cases but rises to 70% when a structural epileptogenic focus is identified.

In analyzing the interpretation of "standard" cerebral MRI vs MRI performed according to epilepsy-dedicated protocols, Von Oertzen and colleagues conclude that the former scans do not yield sufficient diagnostic information to guide prognosis for surgical treatment. In addition to classifying MRI scans as either standard or epilepsy-dedicated, they identified the readers as either nonexpert or expert, where the latter were defined as the neuroradiologists in their epilepsy center, all of whom had greater than 3 years of "epileptological experience." Nonexperts interpreting standard MRI scans in 123 patients reported 61% as normal. Of the 39% of scans reported as showing structural lesions, 7% (n = 8) were said to show HS. By contrast, when the standard MRI scans were re-interpreted by the expert readers, 28% were deemed technically inadequate, 22% were read as normal, and 50% were reported as having structural lesions. Eighteen percent (n = 22) of all scans showed HS. Leaving aside the possibility that the nonexpert radiologists may have read some "false-positive" HS (particularly if some studies were technically inadequate), the expert readers picked up an additional 14 patients whose imaging findings may have placed them in a more favorable outcome category. In fact, if the structural lesions were identified sooner, an earlier referral to an epilepsy center may have been made, possibly resulting in reduced seizure-related morbidity for these patients. Even more dramatically, when expert readers interpreted epilepsy-dedicated MRI scans, 85% of patients with reportedly normal standard MRI were found to have structural lesions. Of those patients who underwent resection, neuropathological diagnosis was correctly predicted by 89% of dedicated MRI reports, but only 22% of "nonexpert" standard MRIs.

COMMENTARY

By 1999 (when this study closed) routine cerebral MRI scans done in the community demonstrated poor sensitivity in diagnosing lesional epilepsy. There is no reason for this to be the case, since an epilepsy-dedicated MRI can be performed on standard 1.5 Tesla scanners with software already installed. The problem of inadequate MRI protocols is compounded by a shortage of neuroradiologists with sufficient experience with epilepsy. Unfortunately, Von Oertzen et al were not able to address the sensitivity and specificity of nonexpert interpretation of dedicated MRI. I suspect that the sensitivity of identifying structural lesions would increase, but there may still be sufficient concerns regarding decreased specificity to warrant systematic investigation of this issue.

More alarmingly, the data in this paper raise the possibility that patients presenting with a first seizure and a subtle (but epileptogenic) structural lesion may not be properly diagnosed. While prudent practice follows the rule of treating the patient, not the scan or EEG in isolation, the threshold for antiepileptic drug prophylaxis is potentially lower if there is knowledge of imaging or EEG abnormalities predisposing to recurrent seizures. A higher neuroimaging standard is needed in evaluating first-time seizures, as well as intractable epilepsy. Dedicated epilepsy MRIs for a first-time seizure could decrease potential morbidity associated with delaying treatment until the epilepsy declares itself. — **ANDY 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.

Clinical Pearls in Differentiating Junctionopathies, Histologic Pearls in Defining IBM

ABSTRACTS & COMMENTARY

Sources: Wirtz PW, et al. Difference in distribution of muscle weakness between myasthenia gravis and the Lambert Eaton myasthenic syndrome. *J Neurol Neurosurg Psychiatry*. 2002;73:766-768; Dahlbom K, Lindberg C, Oldfors A. Inclusion body myositis: Morphological clues to correct diagnosis. *Neuromuscul Disord*. 2002;12:853-857.

Overlap of symptomatology can make differentiation of myasthenia gravis (MG) from Lambert

Eaton myasthenic syndrome (LEMS) challenging. Among 101 patients with MG and 38 with LEMS, clinical features allowing more accurate differential diagnosis are noted below (*see Table*).

LEMS never begins with extraocular muscle weakness, nor does it ever produce weakness limited to the arms. MG generally begins with cranial nerve weakness and progresses caudally, whereas LEMS begins in the legs and progresses cephalad.

Pathologic confirmation of suspected inclusion body myositis (IBM) may also be difficult, as rimmed vacuoles and inflammation can be absent. Additional diagnostic cues would be beneficial. Between 1984 and 2000, tissue diagnosis of sporadic IBM was made in 43 patients who underwent a total of 86 biopsies. Muscle specimens were obtained by open biopsy and included the deltoid (n = 51), vastus lateralis (n = 19), tibialis anterior (n = 5), or other muscles (n = 11). Morphological criteria for IBM were those of Griggs and associates[1] and included invasion of non-necrotic fibers by mononuclear cells, vacuolated muscle fibers, and intracellular amyloid deposits or 15-18 nm tubofilaments. Review of these specimens yielded further morphological clues helpful for accurate diagnosis. All biopsies demonstrated upregulation of major histocompatibility complex class I, and 84 of 86 biopsies contained cytochrome c oxidase-negative (COX-deficient) muscle fibers. All vastus lateralis and tibialis anterior specimens were rimmed-vacuole positive, as were 43 of 51 deltoid biopsies. Even in the absence of inflammation or rimmed vacuoles, COX-negative fibers and major histocompatibility complex class I upregulation makes IBM the diagnosis of exclusion and should prompt rebiopsy to attempt confirmation.

Table

Myasthenia gravis (MG) vs Lambert Eaton myasthenic syndrome (LEMS)

	MG		LEMS	
Initial weakness	Ocular	59%	Limbs	95%
	Bulbar	29%	Bulbar	5%
	Limbs	12%	Ocular	0%
Distribution of weakness at maximal severity	Generalized	68%	Generalized	95%
	Ocular	25%	Limbs	2%
	Oculobulbar	5%	Oculobulbar	0%
	Limbs	2%	Ocular	0%

COMMENTARY

Gene expression profiles may also assist in the differential diagnosis and understanding of inflammatory myopathy including IBM, polymyositis, and dermatomyositis.[2] Using spectrophotometry to measure cellular mRNA concentration, the relative levels of gene expression may be quantified, producing a molecular profile or "signature" for any tissue. Enhanced expression of various genes would underscore their importance in the etiopathogenesis of the disease process. Already successfully applied in the study of various tumors, including B-cell lymphoma, malignant melanoma, oligodendroglioma, colon and breast cancer, this technology correctly classified 10 of 11 patients with inflammatory myopathy, 10 of 12 with Duchenne dystrophy, 11 of 11 with nemaline myopathy, and all 11 controls.[3] Molecular fingerprint technology demonstrates great potential for the advancement of myology and portends significant strides for medicine in general. — **MICHAEL RUBIN**

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CME Questions

4. Late secondary ischemic injury is most likely to occur in which of the following clinical situations?

a. Profound initial ischemic injury
b. Intermediate degrees of ischemia
c. Mild degrees of ischemia
d. When arterial reocclusion follows thrombolysis
e. When there is post-ischemic hyperperfusion

5. Compared to those with normal memory, individuals with superior memorizing ability:

a. have superior verbal IQs.
b. have unique features of brain anatomy.
c. must possess eidetic recall abilities (photographic memory).
d. more commonly use mnemonic strategies.

Correction

In the January 2003 *Neurology Alert*, the CME questions were incorrectly numbered. They should have been numbered 1-3. We regret the confusion this may have caused.

In Future Issues:

A Look at Some Memorable Brains

PHARMACOLOGY WATCH

FDA Issues 'Black Box' Warning Based on WHI Study

The FDA has mandated a "Black Box" warning for all estrogen and estrogen/progestin products for use by postmenopausal women. The new warnings are based on analysis of data from the Women's Health Initiative (WHI) study that was published July 2002. The box warning emphasizes that these drugs have been associated with increased risks for heart disease, heart attacks, strokes, and breast cancer and that they are not approved for heart disease prevention. Wyeth Pharmaceuticals, the manufacturer of Premarin, Prempro, and Premphase, products that were used in the WHI study, are also required to change their indications to: treatment of severe vasomotor symptoms, vulvar and vaginal atrophy associated with menopause, prevention of postmenopausal osteoporosis, and should only be used when the benefit clearly outweighs the risk. The labeling will also be required to include consideration of other therapies for the atrophy and osteoporosis indications, and to recommend use of the lowest dose for the shortest duration possible. While Wyeth's products are the focus of this initial press release and FDA action, all estrogen products will be subject to new labeling. The FDA is also recommending future research to answer questions regarding the risks of lower-dose estrogen products and if other types of estrogens and progestins are associated with lower risk of CVD and breast cancer. The complete press release can be viewed at www.fda.gov.

ALLHAT: Thiazide for Hypertension Treatment

Thiazide diuretics should be considered first-line therapy for hypertension, according to the authors of the ALLHAT study published in December. In a finding that surprised nearly everyone (especially the sponsors of the study) in patients with hypertension and at least one other cardiovascular risk factor, the diuretic chlorthalidone was associated with better cardiovascular outcomes at less cost and with equal tolerability compared to a calcium channel blocker or an ACE inhibitor. ALLHAT enrolled more than 33,000 patients from 623 centers in the United States, Canada, and the US Virgin Islands. Patients were randomized to the calcium channel blocker amlodipine, the angiotensin-converting enzyme inhibitor lisinopril, or chlorthalidone. Mean follow-up was 4.9 years with the primary outcome being combined fatal CHD or nonfatal MI. Secondary outcomes included all-cause mortality, stroke, combined CHD, and combined cardiovascular disease (CVD). The 6-year rate of the primary outcome and all-cause mortality was virtually identical for all 3 drugs. Chlorthalidone was superior to amlodipine in preventing heart failure (10.2% vs 7.7%, RR, 1.38, 95% CI, 1.25-1.52) and was superior to lisinopril for lowering blood pressure and in 6-year rates of combined cardiovascular disease including stroke (6.3% vs 5.6%) and heart failure (8.7% vs 7.7%). With improved cardiovas-

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cular outcomes, lower cost, and equal tolerability, the study concludes that thiazide-type diuretics are superior in preventing one or more forms of CVD and that they should be the preferred agent in antihypertensive therapy, and should be included in all multidrug regimens (*JAMA*. 2002;288:2981-2997). An accompanying editorial calls ALLHAT "one of the most important trials of antihypertensive therapy" and suggests that national guidelines should be changed to emphasize use of thiazide diuretics as initial therapy (*JAMA*. 2002;288:3039-3042).

Candesartan Effective Against Migraines

The angiotensin II receptor blocker candesartan is effective in preventing migraine headaches, according to a new study. Norwegian researchers looked at 60 patients age 18-65 with 2-6 migraines per month. Patients were randomized in a double-blind placebo-controlled crossover study with the main outcome being number of days with headache. Secondary outcomes included use of pain medications and triptans, hours with headache, headache severity, and days lost from work. During the 12-week study, the mean number of days with headache was 18.5 with placebo vs 13.6 with candesartan (P = .001) in the intention to treat analysis (n = 57). Patients were considered a candesartan responder if they noted a reduction of 50% or more of days with headache (18 of 57 patients, 31.6%) or days with migraine (23 of 57 patients, 40.4%). Although this represented a minority of patients, those who did respond benefited from effective migraine prophylaxis. Candesartan's tolerability profile was comparable with placebo (*JAMA*. 2003;289:65-69).

Cough! No Cold Relief from Echinacea

Echinacea offers no benefit in treating the common cold according to a study from the University of Wisconsin. A total of 148 college students with recent onset colds were randomized to an encapsulated mixture of unrefined Echinacea (*E purpurea* herb and root and *E angustifolia* root) 6 times a day on the first day of illness and 3 times a day on the subsequent days up to a total of 10 days. The main outcome was the severity and duration of self-reported symptoms of URI. No statistically significant differences were detected between Echinacea and placebo groups for any of the measured outcomes, which included trajectories of severity over time or mean cold duration. No significant side effects were noted with Echinacea. The study concludes that no detectable benefit or harm could be found with Echinacea treatment for the common cold (*Ann Intern Med*. 2002;137:939-946).

COX-2 Inhibitors and GI Benefits Could Be Overrated

Could the GI benefits of COX-2 inhibitors be overrated? A new study suggests that the COX-2 inhibitor celecoxib is no safer than a combination of diclofenac plus omeprazole with regard to ulcer risk in patients with a history of peptic ulcer disease and arthritis. Researchers from Hong Kong recruited patients with arthritis and NSAID-related bleeding ulcers. After their ulcers had healed, 287 patients who were negative for *Helicobacter pylori*, were randomly assigned to receive celecoxib 200 mg twice a day plus placebo, or diclofenac 75 mg twice a day plus 20 mg of omeprazole for 6 months. Recurrent bleeding ulcer occurred in 7 patients receiving celecoxib and 9 receiving diclofenac/omeprazole (4.9% vs 6.4%). Renal adverse events including hypertension, peripheral edema, and renal failure occurred in 24.3% of patients receiving celecoxib and 30.8% of those receiving diclofenac/omeprazole. The authors suggest that neither regimen offered effective protection against recurrent ulcer complications or renal adverse effects (*N Engl J Med*. 2002;347:2104- 2110).

FDA Actions

Pfizer's new anti-migraine drug, eletriptan (Relpax) has been approved by the FDA for marketing. The drug that is available in 20-mg and 40-mg tablets has been shown to be effective in aborting migraine headaches within 2 hours. The company is marketing a 80-mg tablet in Europe, but the FDA refused to approve the higher dose due to an increase in adverse events.

Montelukast (Singulair), Merck's leukotriene inhibitor, has been approved by the FDA for the treatment of seasonal allergic rhinitis. The drug has been on the market since 1998 for the treatment of asthma in adults and children. This new indication is the first for a leukotriene inhibitor, and creates a new, nonantihistamine treatment modality for this indication. Montelukast was approved for symptoms of seasonal allergic rhinitis in adults and children aged 2 years and older. It is available in 10 mg strength for adults, and a chewable 4 mg or 5 mg strength for children. ■