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INSIDE

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Eosinophilic Neuropathy — Is It In Your Skin?

ABSTRACT & COMMENTARY

By Norman Latov, MD,PhD
Professor of Neurology and Neuroscience, Weill Medical College of Cornell University
Dr. Latov is a consultant for Quest Diagnostics and a stockholder in Therapath.

Synopsis: Patients with eosinophilic neuropathy, associated with primary eosinophilia or the Churg-Strauss syndrome, exhibit cutaneous vasculitis and reduced epidermal nerve fiber density.

Source: Chao, CC, et al. Skin Denervation and Cutaneous Vasculitis in Eosinophilia-Associated Neuropathy. *Arch Neurol* 2007; 64: 959-965.

Peripheral neuropathy is common in patients with the Churg-Strauss syndrome that present with eosinophilia, asthma, and small vessel vasculitis. Neuropathy also occurs in primary eosinophilia, in the absence of Churg-Straus syndrome, but a nerve and muscle biopsy is often required in such cases to determine whether it is caused by vasculitis.

Chao and colleagues examined skin biopsies from 12 patients with neuropathy and concomitant eosinophilia, 6 with primary eosinophilia, and 6 with the Churg-Strauss syndrome. Normal appearing skin was obtained by punch biopsies from the distal calves, and epidermal nerve fiber density was determined by immunocytochemistry, using a monoclonal antibody to the neuronal gene product 9.5. A diagnosis of cutaneous vasculitis was made if there was evidence for both perivascular inflammation and vascular injury. Disruption of vascular integrity was evidenced by the presence of infiltrating leukocytes with discontinuity of the vascular wall, or extravasation of red blood cells.

Mononeuritis multiplex was the most frequent presentation, occurring in 5 of 6 patients in each of the 2 groups, with the others presenting with distal symmetric neuropathy. All 12 improved after therapy with steroids, alone, or in combination with cyclophosphamide or plasmapheresis.

Epidermal nerve fiber density was reduced in 10 patients, 5 with

primary eosinophilia and 5 with the Churg-Strauss syndrome, consistent with the loss of small nerve fibers. All 6 patients with Churg-Strauss syndrome, and 3 of the 6 with primary eosinophilia, fulfilled pathological criteria for definite vasculitis; one primary eosinophilia patient had borderline vasculitis. Perivascular eosinophils were seen in 3 of 6 patients with Churg-Strauss syndrome, and in 2 with primary eosinophilia.

The authors conclude that the neuropathy of primary eosinophilia is commonly associated with small vessel vasculitis, similarly to that seen in the Churg-Strauss syndrome. They also note that pathological analysis of punch skin biopsy may spare patients from a nerve and muscle biopsy, if the analysis confirms the presence of cutaneous vasculitis.

COMMENTARY

The observed reduction of epidermal nerve fiber density in the patients described is not particularly surprising, as all had abnormal EMG and nerve conduction studies. Determination of epidermal nerve fiber density is most useful for diagnosing neuropathy in patients with small fiber disease, or with insufficient involvement of the large fibers to be picked up by electrodiagnostic studies.

Comparison of the nerve fiber density at the distal calf, to that proximally at the thigh, can, in addition, help distinguish between multifocal and distal/symmetric neuropathies. In distal/symmetric neuropathy the nerve fiber loss is more severe at the calf, whereas in multifocal neuropathy or sensory neuronopathy the thigh may be more severely affected. This type of analysis was not done in the current study, but might have revealed more severe reduction of nerve fiber density at the thigh, including in the 2 patients with normal distal nerve fiber densities.

Pathological analyses of skin biopsies can provide clues to the pathogenesis of the neuropathy. Amyloid deposits, as example, can sometimes be seen in skin biopsies from patients with neuropathy and systemic amyloidosis, and the authors previously reported the presence of cutaneous vasculitis in patients with neuropathy and systemic lupus erythematosus. Pathological analysis of skin biopsy may thereby spare the patient from a more invasive nerve and muscle biopsy, in patients suspected to have vasculitis.

The current paper provides support for the hypothesis that eosinophilic neuropathy is caused by vasculitic injury rather than eosinophilic toxicity, although the latter may also contribute to the vasculitis. Primary eosinophilia is a diverse disease, with recent studies implicating such mechanisms as constitutive activation of cellular tyrosine kinases, or secretion of IL5 by clonally expanded T-cells. Potential therapies that more specifically target the underlying mechanisms include mepolizumab, an anti-IL5 antibody, or imatinib mesylate (Gleevec), an inhibitor of tyrosine kinase. It remains to be seen whether these might be more effective therapies for the neuropathies associated with eosinophilia. ■

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Predicting ALS Progression

ABSTRACT & COMMENTARY

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

Synopsis: Muscle Nogo-A may be a useful biomarker for the early diagnosis of ALS.

Source: Pradat PF, et al. Muscle Nogo-A expression is a prognostic marker in lower motor neuron syndromes. *Ann Neurol* 2007;62:15-20.

Harel NY, Strittmatter SM. Nogo-A marks motor neuron disease. Editorial. ibid 1-2.

THE DIAGNOSIS OF AMYOTROPHIC LATERAL SCLEROsis (ALS) is devastating for patient and family

alike. Nevertheless, the ability to predict which patients with lower motor neuron disease will progress to full blown ALS would be beneficial by enabling earlier enrollment into clinical trials, offering added hope, and potentially therapeutic benefit. Thirty-three patients, evaluated at the Paris or Strasbourg Motor Neuron Disease Center between 2003 - 2005 for a purely lower motor neuron syndrome, were followed prospectively over 12 months to determine whether progression to ALS could be predicted by positive Nogo-A expression in muscle biopsy. Lower motor neuron involvement was documented clinically by the presence of weak, wasted, fasciculating muscles, and confirmed electrodiagnostically by reduced motor evoked potential amplitudes on nerve conduction studies, or spontaneous activity (positive sharp waves and fibrillation potentials), or a reduced interference pattern on needle electromyography. At entry, no patient demonstrated upper motor neuron signs (spasticity, hyperreflexia, retained reflexes in weak wasted muscles, Hoffman or Babinski signs, loss of superficial abdominal reflexes), bulbar involvement, respiratory compromise, or sensory signs. All underwent spinal magnetic resonance imaging, sedimentation rate, serum immunoelectrophoresis and immunofixation, anti-GM1 and anti-poliovirus antibodies, and thyroid and parathyroid function. Muscle biopsy, usually of the deltoid (n = 28) unless it was deemed too atrophic, was performed as part of the routine workup, and Nogo-A expression was measured by Western blot techniques. Neurologists blinded to Nogo-A test results performed quarterly neurologic examinations to determine disease progression.

Strikingly, among 17 patients who tested positive for Nogo-A on muscle biopsy, found as early as 3 months following onset, 15 progressed to a definite ALS diagnosis, yielding 91% accuracy, 94% sensitivity, and 88% specificity. Among 16 Nogo-A negative patients, only 1 progressed to ALS over a mean follow-up of 25 months (14-37 months). Final diagnoses in this group included progressive spinal muscular atrophy (n = 6), lumbosacral root compression (n = 4), postpolio syndrome (n = 2), and one each of chronic inflammatory demyelinating polyneuropathy, idiopathic brachial plexopathy, and SMN1-linked spinal muscular atrophy. The authors conclude that muscle Nogo-A expression may accurately and specifically predict progression of lower motor neuron disease to ALS.

COMMENTARY

Were that it were so! Nogo, comprising isoforms Nogo-A, Nogo-B, and Nogo-C, is part of the reticulon family of integral membrane proteins demonstrated to inhibit axonal sprouting and regeneration in the adult nervous system. Though initially found in muscle biopsies from amyotrophic lateral sclerosis but not neuropathy or myopathy patients, suggesting it might be a specific marker for ALS, more recent evidence indicates that it is expressed in a host of neuromuscular disorders including peripheral neuropathies, polymyositis, dermatomyositis and histologically non-specific myopathies (Wojcik S et al. *Acta Myol*. 2000;25:116-118). 20 kDa proteolytic Nogo-A product was also detected in 110/114 (96%) cerebrospinal fluid samples from patients with multiple sclerosis, compared to 0/18 patients with meningo-encephalomyelitis, 0/125 controls with other neurologic diseases, and 0/10 patients with central nervous system autoimmune diseases (Jurewicz A et al. *Neurology* 2007:68:283-287). Nogo-A appears not to be as specific as hoped for. Nevertheless, in the correct clinical setting, it may help predict early diagnosis of ALS. The jury is still out.

Prognosis and Neurological Outcomes after Aneurysmal Subarachnoid Hemorrhage

ABSTRACT & COMMENTARY

By Matthew E. Fink, MD

Synopsis: In spite of great advances in neuroimaging, neurocritical care, and neurosurgical interventions for the diagnosis and treatment of aneurysmal subarachnoid hemorrhage (SAH), it is uncertain if case morbidity and mortality have significantly declined.

Sources: Rosengart AJ, et. al. Prognostic factors for outcome in patients with aneurysmal subarachnoid hemorrhage. *Stroke* 2007; 38:2315-2321.

Tanno Y, et al. Rebleeding from Ruptured Intracranial Aneurysms in North Eastern Province of Japan. A cooperative study. *J Neurol Sci* 2007;258:11-16.

Advances in CT and MRI technology have made the rapid diagnosis of ruptured intracranial aneurysm a routine matter in most hospitals, and the proliferation of advanced neurocritical care units in neurosurgical referral centers across the U.S. have allowed for referral of most patients to specialized

centers that have the most advanced knowledge and technology (including endovascular coiling and stenting) to treat virtually every type of patient with a ruptured intracranial aneurysm. It would be expected, therefore, that these dramatic advances in neurosurgical care would be translated into better outcomes for patients admitted with aneurysmal SAH. Two recent studies, however, have looked at the factors that determine prognosis and outcome, and lead us to question how much real progress we have made in improving the clinical outcome of these patients, in spite of great technological advances that have been applied to their care.

Rosengart and colleagues performed an analysis of a large cohort of 3567 patients, who were enrolled in 4 different randomized trials of tirilizad at neurosurgical centers around the world, between 1991 and 1997. Because there was no significant difference in outcomes between the tirilizad and placebo groups, they were combined in order to have the largest possible cohort to perform a Cox proportional hazards regression analysis for variables that would have an impact on outcomes, as measured by the Glasgow Outcomes Scale (GOS) at three months. The GOS was further simplified into a binary dependent variable — good outcome vs poor outcome. Poor outcome was defined as dead, vegetative, or severely disabled. All patients had their aneurysms treated with open surgical clipping; there were no endovascular interventions in this group. The investigators analyzed a comprehensive list of factors, both preoperative as well as in-hospital factors, that might have an impact on outcome, and converted the associations to hazard ratios that would predict "poor" outcome on the GOS. The reference group used for calculation of the odds ratios was male, age 18-29, World Federation of Neurological Surgery grade 1, no or local thin SAH on admission CT scan, and a ruptured aneurysm < 12 mm in size located on the internal carotid artery. The significant variables identified in the multivariable logistic regression model were increasing age, admission neurological grade, posterior circulation aneurysm, larger aneurysm size, thick clot on CT, intracerebral hematoma, intraventricular hematoma, elevated systolic pressure, previous diagnosis of hypertension, myocardial infarction, liver disease, or previous SAH, temperature > 38° C, symptomatic vasospasm, and cerebral infarction. The use of prophylactic or therapeutic hypervolemia or hypertension was associated with a lower risk of unfavorable outcome. Overall, 70% of the entire group was reported as "good" outcome; this compared to an earlier Finnish study from an earlier decade, using similar statistics, that showed an overall "good" outcome of 68% (Niskanen, et. al. *Acta Neurochir* 1993; 123:25-32).

The Rosengart study did not address the important issue of early aneurysm re-rupture as a prognostic factor, a topic that was specifically studied by Tanno, et al. In a retrospective chart review of 5612 cases of ruptured intracranial aneurysms in Japan, Tanno, et al identified 181 patients with rebleeding after hospitalization, before the aneurysm could be secured. They noted that rebleeding occurred in 65 (35.9%) within 3 hours and 88 (48.6%) within 6 hours of the initial SAH. The level of consciousness abruptly declined at the time of rebleeding and the diagnosis was made by repeat CT scanning. They also noted that rebleeding occurred more frequently during cerebral angiography (29 patients; 20%) and much less frequently during CTA or MRA (a single case). Systolic BP was noted to be 120-140 immediately prior to the re-bleeding episode. Of the patients who suffered early rebleeding, 60% died within 3 months following SAH.

COMMENTARY

Advanced imaging with CT, MRI and MRA have improved and simplified the early diagnosis of aneurysmal SAH, and computerized navigation and microsurgical techniques, along with endovascular coiling have dramatically altered the neurosurgical approaches to ruptured intracranial aneurysms. Neurocritical care specialists have concentrated their efforts to improve the care of these patients with special attention to issues surrounding vasospasm, cerebral perfusion pressure, intracranial pressure, and neuroprotection. But have these technical advances improved the overall outcome for these patients? At the present time, we are unable to answer that question, but the studies by Rosengart and Tanno suggest that the major factors that determine survival and recovery are present at the time of admission and there seems to be little we can do to modify these factors. Early re-rupture, which carries a high mortality, can be addressed with faster and safer diagnostic techniques using CT angiography, followed by immediate aneurysm obliteration. Early use of antifibrinolytic drugs should be investigated as a possible method to reduce early re-rupture. Aggressive blood pressure lowering, prior to aneurysm obliteration, should also be investigated as a possible therapy. Other risk factors, as outlined by Rosengart et al, should be systematically studied for any innovative treatment approaches that might modify their influence and reduce their

impact on outcome. And finally, we need more population-based studies of case morbidity and mortality to assess our overall success, or failure, in the treatment of this devastating disease.

Levodopa Response and Prognosis in Parkinson's Disease

ABSTRACT & COMMENTARY

By Claire Henchcliffe, MD, DPhil

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Dr. Henchcliffe reports no financial relationship to this field of study.

Synopsis: Patients with Parkinson's disease taking levodopa were divided into groups with (i) moderate-severe fluctuations and (ii) stable response. Despite a longer disease course in moderate-severe fluctuators, progression in the late stages and autopsy findings were similar between groups, suggesting non-linear disease progression.

Source: Kempster PA, et al. Patterns of levodopa response in Parkinson's disease: a clinico-pathologic study. *Brain*. 2007;130:2123-2128.

THE AUTHORS IDENTIFIED 97 AUTOPSY-PROVEN Parkinson's disease (PD) cases from the Queen's Square Brain Bank between 2001 and 2006, all with long-term levodopa treatment and rigorous clinical documentation. Clinical features were evaluated by chart review. Cerebral pathology was determined by: synuclein antibody-mediated identification of Lewy bodies, in the substantia nigra, transentorhinal and cingulate cortex, and neocortex of the second frontal gyrus, superior temporal gyrus, and inferior parietal cortex, as well as examination for Alzheimer-type pathology and other changes. Cases comprised 32 women and 65 men, with mean age at diagnosis 61.7 ± 10.3 years (range 43-80). Motor fluctuations developed in 64%, and dyskinesias in 62%. Of the 35 cases without motor fluctuations, only 14% developed dyskinesias. Cases were divided into non-fluctuators, mild fluctuators, and moderate-severe fluctuators. Moderate-severe fluctuators had younger age of onset (57.9 ± 10.7 vs 66.4 ± 8.3 years, $P < 0.001$), and longer disease course (17.6 ± 5.9 vs 9.9 ± 6.4 years, $P < 0.001$), with similar age at death (75.4 ± 9.4 vs 76.3 ± 8.3 years) compared with non-fluctuators. Time from diagnosis to starting levodopa was not significantly different between the groups, but moderate-severe fluctuators took higher maximum levodopa doses than non-fluctuators (1041 ± 450 vs 549 ± 267 mg daily, $P < 0.001$). Incidence of pre-designated milestones of late disease, comprising frequent falls (36% vs 31%), visual hallucinations (64% vs 57%), cognitive disability (53% vs 63%), and moving to residential care (44% vs 63%), did not significantly differ between groups. Mean interval from any of these milestones to time of death was similar between groups (frequent falls: 3.9 vs 3.6 years; visual hallucinations: 4.5 vs 3.9 years; cognitive disability: 3.2 vs 3.0 years; residential care: 2.9 vs 2.5 years). Autopsy examination revealed evidence of moderate-severe loss of substantia nigra neurons and associated Lewy bodies in all, and neocortical Lewy bodies in 67%. Patterns of Lewy body distribution were not different between the groups. Alzheimer-type pathology was seen in 54% cases, and cerebrovascular pathology and amyloid angiopathy were also observed in both groups.

COMMENTARY

One aim of the present study was to address whether differences in pathology might explain the well-documented heterogeneity in levodopa response seen in PD. However, the authors found no pathologic correlates with the distinct patterns of levodopa response they chose to examine, defined by motor fluctuations. As they point out, post mortem study may simply be too late in the disease to discern differences between groups that might have been significant earlier. In addition, confining study to Lewy body pathology and to this restricted set of brain regions might be insufficient to detect more subtle differences between PD subtypes. That being said, this article presents some fascinating data that require further understanding, and it underlines gaps in our concept of PD progression. Moderate-severe fluctuators had longer disease duration, implying slower progression, yet late disease milestones occurred at a similar time interval before death as in the non-fluctuators. This suggests that in late disease, progression is similar in both groups (i.e., speeds up in non-fluctuators). Importantly, this challenges the concept of a linear disease course, and the authors suggest a likely interaction with the aging process. Despite limitations inherent in this type of study, these findings raise major questions about our understanding of PD pathophysiology. The study also emphasizes the need

for improving treatment in late disease, when many symptoms are not dopamine-responsive. ■

Neuroimaging in the Evaluation of Headaches During Pregnancy

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD
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Dr. Jamieson is a consultant for Boehringer Ingelheim and Merck, and is on the speaker's bureau for Boehringer Ingelheim, Merck, Ortho-McNeil, and Pfizer.

Synopsis: Emergent neuroimaging studies revealed underlying headache pathology, both in the brain and in sinuses, in 27% of pregnant women with headaches.

Sources: Ramchandren S, et al. Emergent headaches during pregnancy: Correlation between neurological examination and neuroimaging. *Am J Neuroradiol* 2007; 28:1085-1087.

Melhado EM, et al. Headache during gestation: evaluation of 1101 women. *Can J Neurol Sci* 2007;34(2):187-192.

Pregnant women frequently complain of headaches, with the prevalence of headaches during pregnancy reported to be as high as 35%. Women of childbearing age represent the group most afflicted with common primary headache disorders such as migraine and tension-type headaches. During pregnancy and the post-partum period, women may have new onset headaches that are usually primary, but some of these new headaches may be secondary to cerebrovascular disorders or mass lesions. In a prospective evaluation of more than a thousand pregnant women with a headache history, Melhado et al (2007) found that headaches during gestation were due to migraine in over 80% of women with a pre-gestational headache history. Generally, these headaches improved or resolved after the onset of the second trimester. However, in the rare women with a new onset headache during pregnancy, over half had a secondary headache. Less than half of pregnant women with a new onset headache, who had no prior headache history, ended up having a primary headache disorder.

Because the care of a pregnant woman must address the health of both the mother and the fetus, evaluation of the pregnant woman with a headache should focus on the most likely headache diagnosis, while ruling out an ominous cause. Ramchandren et al (2007) investigated the demographic factors, clinical presentations, and examination findings of pregnant women who presented with headache to the emergency department of an urban academic medical center. The authors hypothesized that abnormal findings on neurological examination would be predictive of an intracranial pathological condition on acute neuroimaging studies. The authors reviewed clinical and radiological variables on 63 pregnant women (median age, 26 years; range, 15-41 years) with headache. An odds ratio was generated to examine the likelihood of having an intracranial pathological condition in patients with neurological abnormalities on examination (abnormalities of mental state, cranial nerves, motor, sensory, gait, coordination and/or reflexes). Multivariate logistic regression analysis examined clinical, historical, and examination factors as predictors of a pathological condition on emergent neuroimaging studies.

The mean age of the 63 women was 25.9 years with a mean number of previous pregnancies of 2.2. The mean gestational age was 24 weeks (SD = 9). Multiparous African-American women constituted 63% of the subjects. Headaches were generally dull or throbbing, bilateral, and frontal. They were frequently accompanied by nausea, vomiting, photophobia, and phonophobia. A CT scan was obtained in 86% of women; an MR imaging study was obtained in 60%; almost half the pregnant women had both studies. Magnetic resonance venography and angiography were performed infrequently. While 49% of studies were normal and another 24% of studies found an incidental finding, unrelated to the headache, a pathological condition was found in 17 out of the 63 women. While 5 of these 17 women had sinusitis, 4 had cerebral venous thrombosis and 4 had reversible posterior leukoencephalopathy. Pseudotumor cerebri and intracranial hemorrhage were each found in 2 women.

Of the 26 patients who had focal findings on neurological examination, 10 had pathological neuroimaging findings. The abnormal findings on neurological examination of these women with pathological neuroimaging included mental status abnormalities, sensory abnormalities, seizures, cranial nerve deficits, and pathologic reflexes. Only one of the 4 women with reversible posterior leukoencephalopathy on neuroimaging had a non-focal neurological examination. Conversely, of the 17 patients with a pathological neuroimaging finding (including 5 with sinusitis), 7 had normal neurological examinations.

The odds of having an abnormal neuroimaging study were 2.7 times higher in those with abnormal results on

neurological examination, compared to those with normal results, but because of a wide confidence interval, this finding was not statistically significant. While there were no demographic or clinical variables that were significantly predictive of intracranial pathological condition on emergent neuroimaging studies, abnormal mental status and increased hours of headache duration were suggestive of abnormal neuroimaging.

COMMENTARY

Most pregnant women with an acute headache and a prior headache history have a primary headache such as migraine or tension-type headache. A pregnant woman who presents for emergent evaluation with an acute headache should have a history and neurological examination focusing initially on the most common causes of primary headaches. However, when there is lack of a prior headache history and an abnormality on neurological examination, brain imaging should be performed to rule out a pathological cause of headache. In this paper, 12 out of 63 pregnant women with a headache had significant brain pathology, as opposed to sinus pathology, on neuroimaging. The authors of this study note that ordering neuroimaging studies on a pregnant woman often causes unnecessary concern about fetal effects, but that this fear is generally not warranted. They point out that the amount of fetal radiation exposure from a 10-section CT-scan is well below the amount associated with fetal abnormalities. While an abnormality on neurological examination increases the likelihood of finding a pathological cause for headache on imagining, the decision to order neuroimaging studies should not be based on the neurological examination alone. Even if the neurological examination is normal, the onset of a new headache in a pregnant woman is ominous and may require neuroimaging to rule out a pathologic etiology.

Paroxysmal Atrial Fibrillation: An Underdiagnosed Cause of Stroke?

ABSTRACT & COMMENTARY

By Dana Leifer, MD

Associate Professor, Neurology, Weill Medical College, Cornell University

Dr. Leifer reports no financial relationship relevant to this field of study.

Synopsis: Long-term monitoring is likely to detect atrial fibrillation in stroke patients with frequent atrial premature beats.

Source: Wallmann D, et al, Frequent atrial premature beats predict paroxysmal atrial fibrillation in stroke patients: An opportunity for a new diagnostic strategy. *Stroke* 2007;38:2292-2294.

Approximately 30% of ischemic strokes do not have a definite etiology (cryptogenic) even after diagnostic evaluations that are considered comprehensive by current standards. It is often thought that many of these strokes are embolic in origin. One possible explanation for some of these cryptogenic strokes is paroxysmal atrial fibrillation (AF). Paroxysmal AF may not be detected by conventional cardiac monitoring, which is usually limited to a 24-hour Holter monitor or to cardiac telemetry while the patient is hospitalized.

One recent study found that new AF was diagnosed on the admission electrocardiogram in 11 of 149 patients with an acute stroke or transient ischemic attack (TIA) and without a prior history of AF. AF was identified by 24-hour Holter monitors in an additional 7 patients and by 7-day event loop recordings in another 5 patients (*Stroke* 2004;35:1647). These results suggest that more extensive cardiac monitoring is likely to identify atrial fibrillation in more patients than conventional monitoring. It would be helpful to limit such intensive recording to patients who are at increased risk to have paroxysmal AF.

In this background, Wallmann et al prospectively studied ischemic stroke patients without known AF. They had previously found that the presence of frequent atrial premature beats (APBs) was associated with an increased incidence of paroxysmal AF in acute ischemic stroke patients. In their new study, they stratified patients for the presence or absence of frequent APBs (≥ 70 per 24 hours). Patients were excluded from the study if atrial fibrillation was found on a 24-hour ECG recording or documented by other means during their admission. Patients were also excluded if they had severe aphasia, other severe cognitive deficits, or a life expectancy of less than 6 months. One hundred and twenty-seven patients were enrolled and underwent 7-day event-recorder monitoring at 0, 3, and 6 months after their stroke.

The chief finding was that paroxysmal AF was found in 26% of patients with frequent APBs (13/50) and in only 6.5% of the remaining patients (5/77). This finding was highly significant with $P = 0.0021$. Multivariate analysis, which looked at 12 other clinical variables, demonstrated that the presence of frequent APBs was the only independent predictor of paroxysmal AF ($P = 0.01$). Of the patients with frequent APBs, 8% were found to have AF on the first 7-day event-recorder, another 12%

on the second one, and another 6% on the third one.

COMMENTARY

These results are important because the presence of atrial fibrillation in stroke patients is generally considered to be a strong indication for oral anticoagulation unless there is a clear contraindication. The results, therefore, suggest that more prolonged monitoring than is generally done may be appropriate, especially in patients with frequent APBs, although AF was even detected in a small percent of patients without frequent APBs.

As the authors correctly point out, however, the presence of AF does not necessarily mean that it is the cause of the patient's stroke, and the value of anticoagulation has not been tested in patients who have been found to have AF only on the type of long-term monitoring done in this study. As the authors suggest, a definitive answer to the question of optimal treatment for such patients would require new clinical trials. Nevertheless, in the absence of such trials, available data about the benefit of anticoagulation in patients with AF suggest that anticoagulation should be considered seriously even if AF is detected only with long-term monitoring. ■

CME Questions

1. Pathological analysis and determination of epidermal nerve fiber density, in punch skin biopsies at the calf and thigh, is useful for which of the following:

a. Making a diagnosis of small fiber neuropathy
b. Differentiating between distal/symmetric and multifocal neuropathy
c. Diagnosing cutaneous vasculitis
d. All of the above
e. None of the above.

2. Nogo-A (is)

a. specific and diagnostic of amyotrophic lateral sclerosis
b. predicts with 100% accuracy progression of lower motor neuron disease to amyotrophic lateral sclerosis
c. has been reported in a host of neuromuscular diseases
d. has been reported in the serum of amyotrophic lateral sclerosis patients
e. none of the above is true

3. Development of moderate to severe motor fluctuations in Parkinson's disease is associated with all of the following except:

a. disease duration
b. maximum levodopa dose
c. more rapid disease progression
d. younger age of onset
e. development of dyskinesias

4. The following factors at time of admission increase the risk of poor outcome after aneurysmal SAH.

a. advanced age
b. thick blood clot on CT scan
c. posterior circulation aneurysm
d. intraventricular hemorrhage
e. poor clinical grade
f. all of the above

5. In a pregnant woman with a headache which of the following is true?

a. Imaging of the brain should never be performed unless there is a motor or cranial nerve deficit on neurological examination.
b. Imaging of the brain should be considered even if the neurological examination is normal.
c. Migraine is the most common cause of new onset headache in a woman without any pre-gestational history of headaches.
d. CT scanning of the brain of pregnant women should almost never be performed because of radiation risk.
e. Headaches are very rare during pregnancy and almost always indicate underlying serious pathology.

6. What percentage of stroke patients with frequent atrial premature beats but no prior history of atrial fibrillation was found to have atrial fibrillation with long-term monitoring?

a. 6
b. 15
c. 26
d. 53

Answers: 1. (d) 2.(c) 3.(d) 4.(f) 5.(b) 6.(c)

Upcoming Symposium

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In Future Issues:

Cognitive Dysfunction after Heart Surgery

PHARMACOLOGY WATCH

Supplement to Clinical Cardiology Alert, Clinical Oncology Alert, Critical Care Alert, Infectious Disease Alert, Internal Medicine Alert, Neurology Alert, OB/GYN Clinical Alert, Primary Care Reports, Travel Medicine Advisor.

Oral Anticoagulant + Antiplatelet Therapy = Danger

In this issue: *Adding an anticoagulant to aspirin is of no value in patients with peripheral artery disease, older adults with coronary disease benefit from aggressive statin therapy, simvastatin may reduce the risk of dementia and Parkinson's disease by as much as 50%, MiraLAX is safe for long-term use in patients with chronic constipation, the FDA greenlights Avandia, brings back Zelnorm for limited use, and recommends approving Evista for breast cancer prevention.*

Patients with peripheral artery disease are at high risk for cardiovascular complications. Antiplatelet drugs are routinely prescribed for these patients, but is adding an oral anticoagulant of value? No, according to a new study. In fact, the combination may be dangerous. More than 2,100 patients with PAD were randomly assigned to antiplatelet therapy with an oral anticoagulant or to antiplatelet therapy alone. The first coprimary outcome was myocardial infarction, stroke, or death from cardiovascular causes. The second coprimary outcome was myocardial infarction, stroke, severe ischemia of the peripheral or coronary arteries leading to urgent intervention or death from cardiovascular causes. After an average followup of 35 months, the first coprimary outcome occurred in 132 of 1080 patients receiving combination therapy (12.2%) and 144 of 1081 patients receiving antiplatelet therapy alone (13.3%) (RR 0.92; 95% CI, 0.73 to 1.16; $P = 0.48$). The second coprimary outcome occurred in 172 patients receiving combination therapy (15.9%) compared to 188 patients receiving antiplatelet therapy alone (17.4%) (RR 0.91; 95% CI, 0.74 to 1.12; $P = 0.37$). Life-threatening bleeding occurred in 43 patients receiving combination therapy (4.0%) as compared to 13 patients receiving antiplatelet therapy alone (1.2%) (RR 3.41; is 95% CI, 1.84 to 6.35; $P < 0.001$). The authors conclude that adding an oral anticoagulant to antiplatelet therapy in patients with PAD was not more effective than antiplatelet therapy alone in preventing major cardiovascular complications, but was associated with an increase in life-threatening bleeding (*N Engl J Med* 2007; 357: 217-227). ■

High-Dose Statin Therapy, Value for Older Adults

Aggressive lipid lowering with high-dose statin therapy may be of value in older adults with stable coronary disease. The multicenter study from the United States included 3,809 patients 65 years or older with coronary artery disease and cholesterol levels less than 130 mg/dl who were randomized to receive atorvastatin 10 mg or 80 mg. Patients on low-dose atorvastatin achieved average cholesterol levels of 100 mg/dl versus 70 mg/dl for high dose therapy. The primary endpoint was occurrence of first major cardiovascular event such as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitated cardiac arrest, or fatal or nonfatal stroke. Patients treated with high-dose atorvastatin were found have a 2.3% absolute risk reduction and a 19% relative risk reduction for the primary endpoint (hazard ratio 0.81 [95% CI, 0.67 to 0.98]; $P = 0.032$). Mortality rates were

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lower for CHD, nonfatal non--procedure-related myocardial infarction, and stroke in the high-dose group. High-dose therapy was not associated with elevated creatine kinase levels. The authors conclude that treating older patients with coronary heart disease more aggressively to reduce low-density lipoprotein cholesterol levels provides additional clinical benefit (*Ann Int Med* 2007;147: 1-9). ■

Simvastatin, Best for Parkinson's Disease

Simvastatin, not atorvastatin or lovastatin, is associated with a dramatically reduced risk of dementia and Parkinson's disease (PD) according to a study from Boston University and VA database of 4.5 million individuals (95% men). In the observational study, over 700,000 subjects took simvastatin, nearly 54,000 took atorvastatin, and over 54,000 patients were prescribed lovastatin. Three models were used to evaluate the data, adjusting for covariates associated with dementia or Parkinson's disease. The first model was adjusted for age; the second model adjusted for 3 known risk factors for dementia: hypertension, cardiovascular disease, or diabetes; and the third model adjusted using the Charlson index, an index that provides broad assessment of chronic disease. Using the third model, the hazard ratio for dementia was 0.46 for simvastatin (CI 0.44-0.48, $P < 0.0001$) and 0.91 for atorvastatin (CI 0.80-1.02, $P = 0.11$). Lovastatin was not associated with a reduction in the incidence of dementia. The hazard ratio for newly acquired Parkinson's disease was 0.51 for simvastatin (CI 0.49-0.55, $P < 0.001$). There was no reduction in PD with atorvastatin or lovastatin. The degree of risk reduction utilizing the other models was similar with simvastatin. The authors conclude that simvastatin is associated with a strong reduction in the incidence of dementia and PD, while atorvastatin is associated with a modest reduction in incidence of dementia and Parkinson's disease that shows a trend toward significance (*BMC Med* published online July 19, 2007). The surprising finding suggests a difference between simvastatin and atorvastatin out of proportion to their cholesterol lowering effects, which the authors suggest may be due to the ability of simvastatin to cross the blood brain barrier more readily than other statins. ■

Polyethylene Glycol for Chronic Constipation

Long-term use of polyethylene glycol is safe and effective for chronic constipation according to the results of a new study from Alabama. More than 300 patients were randomized to receive polyethylene glycol 3350 (MiraLAX) in a single 17 g dose per day or placebo for 6 months. The primary endpoint of improvement of constipation on an objective scale was reached in 52% of the PEG patients and 11% placebo patients ($P < 0.001$). Similar efficacy was seen in a subgroup of 75 elderly patients. There were no significant adverse events other than diarrhea, flatulence and some nausea associated with PEG. The authors conclude that PEG laxative is safe and effective for use in patients with chronic constipation for up to 6 months (*Am J Gastroenterol* 2007;102:1436-1441). The study is particularly important because MiraLAX is now available over-the-counter and long-term use by patients with chronic constipation is likely. ■

FDA Actions

The FDA's Oncologic Drugs Advisory Committee, on a narrow vote, recommended approval of raloxifene (Evista) for the indication of breast cancer prevention in high risk women. The approval was based on data from the Study of Tamoxifen and Raloxifene (STAR) trial, which showed a reduction of 4 cases of breast cancer per 1,000 women (50% relative risk reduction), although it was not as effective as tamoxifen in preventing noninvasive breast cancers. Similar findings were seen in the Raloxifene for Use for The Heart (RUTH) trial although this trial revealed a higher risk of fatal stroke and blood clots with raloxifene. The FDA generally follows its advisory committee recommendations. Raloxifene is already approved for the prevention of osteoporosis.

The FDA has approved restricted use of tegaserod (Zelnorm) for the treatment of irritable bowel syndrome with constipation and chronic idiopathic constipation in women under the age of 55 who meet certain criteria. The drug was taken off the market earlier this year when it was linked with a higher risk of cardiovascular events including heart attack, stroke, and unstable angina. Patients must have no history of heart disease and must be in critical need of the drug. Prescribing will be under an investigational new drug protocol program that has been set up by the FDA.

Rosiglitazone (Avandia-GlaxoSmithKline) is associated with an increase risk of heart failure and myocardial infarction. Despite this, the FDA's Endocrinologic and Metabolic Drugs Advisory committee along with the Drug Safety and Risk Management Advisory Committee has advised that the drug stay on the market, albeit with increased warnings. Type 2 diabetes patients who are on insulin for those with heart disease are not the candidates for the drug. The FDA will render a final decision on the drug this fall. ■