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INSIDE

Next Generation Migraine Drugs?

ABSTRACT & COMMENTARY

Source: Olesen J, et al. *N Engl J Med*. 2004;350:1104-1110.

THE ACCUMULATED EVIDENCE THAT 5-HT (SEROTONIN) PLAYS A role in migraine ultimately led to the development of the 5-HT1B/1D receptor agonists. Further research into the mechanism of action of these drugs then led to the discovery of other vasoactive and neuroinflammatory peptides. Several targets have emerged as promising. Calcitonin gene-related peptide (CGRP) is a neuropeptide that is a potent vasodilator of cerebral and dural vessels. CGRP has been shown to be elevated during a migraine and infusion of CGRP can induce a migraine. CGRP antagonists have been obvious agents to pursue. Olesen and associates report on a phase II study of BIBN 4096 to evaluate the safety and efficacy of a first in class non-peptide, parenteral CGRP-receptor antagonist.

A total of 126 patients with acute moderate-to-severe migraine without aura aged 18-65 with 1-6 migraines per month were enrolled. Besides placebo, a range of intravenous doses (.25, .5, 1, 2.5, 5, 10 mg) were studied. A group-sequential adaptive treatment-assignment design was chosen to compare relatively few patients across this wide range of doses. The primary end point was "headache response" defined as the reduction in severe or moderate headache to mild or no headache at 2 hours. Several secondary end points were also measured such as 24 hours sustained pain relief; relief of nausea, vomiting; clinical disability; use of rescue medication; and rates of adverse events. The group sequential analysis yielded the 2.5 mg dose as the optimal one. At this dose the 2-hour pain relief response was 66% vs 27% for placebo ($P < 0.001$). The recurrence rate was 19% for the 2.5 mg dose vs 46% for placebo. The use of rescue meds was lower across all doses of BIBN 4096. The adverse events were higher in the treatment group 20% vs 12% (P value not provided). The most frequent complaint (8% vs 0%, no P value provided) was paresthesias. No serious side effects were reported. Overall Olesen et al conclude that as a "proof-of-concept" study, intravenous BIBN-4096- a first in class CGRP receptor antagonist, is both safe and effective.

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COMMENTARY

Since, the world needs more migraine drugs, this trial should be seen as hopeful for an emerging new class of treatment. Several points, some of which Olesen et al raise, are worth reiterating here. The current study was small and we do not really know how to compare it with the thousands of patients studied with triptans. Sumatriptan delivered subcutaneously demonstrates 2-hour pain relief efficacy results in the 70-80% range. Would BIBN-4096 need to compete with those numbers? Probably not, especially if the mechanism of action and the clinical results proved synergistic. The fact that the drug does not appear to have vasoconstrictive effects could prove to be a major distinguishing feature from almost every other acute migraine medication on the market. Furthermore, treatment effect was seen as far as 6 hours into the attack, and this could prove quite an advantage over currently approved remedies. Now that Boehringer Ingelheim has a dose to move forward we look ahead to larger more comprehensive phase III data.

— **JEFFERY REICH, MD**

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Myasthenia Gravis 2004

ABSTRACTS & COMMENTARY

Sources: Monsul NT, et al. The effect of prednisone on the progression from ocular to generalized myasthenia gravis. *J Neurol Sci*. 2004;217:131-133; Guillermo GR, et al. Response of thymectomy: Clinical and pathological characteristics among seronegative and seropositive myasthenia gravis patients. *Acta Neurol Scand*. 2004;109:217-221; Koopman WJ, et al. Prediction of aspiration in myasthenia gravis. *Muscle Nerve*. 2004;29:256-260.

DOES PREDNISONE, ADMINISTERED EARLY IN THE course of ocular myasthenia (OMG), affect its progression to generalized disease? Fifty-six patients with OMG were followed for a minimum of 2 years were retrospectively evaluated to address this question. Diagnosis of OMG was clinical and confirmed with EMG, anti-acetylcholine receptor antibody titers, edrophonium test, and ice or sleep test. Patients were excluded if they were younger than 16 years of age or had a thymoma or thymectomy. Pyridostigmine had been administered to all and prednisone was added, 40-60 mg/d initially followed by a 3-6 month taper, if symptoms persisted. Patients were included in the prednisone-treated group if they had received at least 3 months of prednisone within 2 years of diagnosis, whereas those who did not fulfill this criteria were included in the non-prednisone-treated group for purposes of analysis. Statistical analysis was provided by the 2-tailed t-test and chi square analysis.

Among the 56 patients, 27 were in the prednisone-treated group and 29 in the non-treated group. Age, gender, and receptor antibody positivity were comparable in both groups. Significantly, only 3 prednisone-treated patients (11%) developed generalized disease compared to 10 (34%) in the non-treatment group ($P = 0.04$). None of the prednisone-treated patients developed diabetes, hypertension, compression fracture, ulcer, or infection, although mild edema and weight gain were reported in some. These results are promising and warrant larger prospective trials to answer the question definitively.

Do seronegative myasthenia gravis patients benefit from thymectomy as much as do seropositive patients? Does their thymic pathology differ? Using parametric and nonparametric tests for statistical analysis, 57 seropositive patients were compared to 14 seronegative cases, all of whom had been thymectomized between 1987 and 1997. Similar response rates were seen in both groups. Remission was achieved in 21% in both, with improvement in 30% (n = 17) and 36 % (n = 5), respectively; no change in 44% (n = 25) and 36% (n = 5),

respectively, and worsened in 5% (n = 3) and 7% (n = 1), respectively. Seropositive patients were older, mean age 42.9 years vs. 32 years for seronegative patients (P = 0.01), and demonstrated a higher frequency of thymoma, 9% (n = 5) vs none in the seronegative group. Prognosis is similar regardless of antibody status.

Which test might best predict aspiration risk in myasthenia gravis (MG) patients? Twenty MG patients with dysphagia, 10 men and 10 women, participated in a comparison study of 4 noninvasive bedside tests to assess such risk. Testing included a self-directed questionnaire (SDQ, 14 questions evaluating dysphagia), a bedside neurological exam performed by a neurologist who then predicted presence or absence of aspiration risk, the quantitative MG (QMG) score, and a bedside speech pathology assessment. All assessments were performed over a 4-hour period and assessors were blinded to the results of the other tests. Videofluoroscopic assessment of swallowing served as the gold standard for comparison and statistical analysis was performed by independent t-tests, linear regression analysis, and Fisher's exact test.

Two SDQ questions correlated with aspiration: Do you have a hard time moving food or liquids around in your mouth? and: Does it hurt for you to swallow? Neurological examination prediction also correlated with aspiration as did the bulbar subset of the QMG score. However, total QMG score was less useful as was speech pathology evaluation. Simple bedside tests appear to be useful predictors of aspiration but these findings require confirmation in larger studies.

COMMENTARY

Despite the commonality of anti-acetylcholine receptor antibodies (AChR Ab) in seropositive myasthenia gravis (SPMG), it appears to be a rather heterogeneous disease, both from the perspective of thymic pathology and based on presence of serum anti-titin antibodies. Thymic hyperplasia is more common in women, with early age of onset and high titer antibodies, whereas thymoma is equally common in both sexes and is associated with severe disease. Absence of any thymic pathology combined with positive anti-titin antibodies identifies a group with older age of onset (mean, 65 years) and intermediate levels of AChR Ab levels.

Family members are at significantly increased risk, 2-4%, of developing myasthenia compared to the general population, and twin studies, though limited, also support a genetically complex mode of inheritance. Involvement of the HLA complex, including class I alleles B8 and A1, class II alleles DR3 and Dw3, HLA-linked genes including complement C4 and TNF-alpha, and more recently the HLA-DR3 B8 A1 haplotype, associated with MG and thymic hyperplasia, provide further evidence for the direct effect of genetic factors in the development of myasthenia gravis. Interestingly, DR3 which is positively associated with MG and thymic hyperplasia, and DR7 which is negatively associated, show a reverse association in patients with myasthenia, no thymic abnormalities and positive anti-titin antibodies where DR7 is increased and DR3 decreased.

Which candidate gene might influence genetic susceptibility to myasthenia? CHRNA,[1] a gene that codes for the alpha subunit of the muscle acetylcholine receptor, seems a good bet given that it contains the main immunogenic region against which most antibodies are directed. It is directly involved in acetylcholine binding, and it presents the only functional polymorphism known at the protein level in the alpha subunit.

— MICHAEL RUBIN

Reference

1. *J Autoimm*. 2003;21:105-110.

Lack of Inflammatory Pathology in Early Multiple Sclerosis Lesions

ABSTRACT & COMMENTARY

Source: Barnett MH, JW Prineas. Relapsing and Remitting Multiple Sclerosis: Pathology of the Newly Forming Lesion. *Ann Neurol*. 2004;55:458-468.

BARNETT AND PRINEAS DESCRIBE THE PATHOLOGICAL and clinical findings in 12 patients with relapsing-remitting multiple sclerosis (RRMS), who died shortly after the onset of a relapse. In their evaluation of acute symptomatic lesions, they documented pathological changes not previously associated with new lesion formation, namely, extensive oligodendrocyte apoptosis and microglial activation in 7 patients. In such acute cases there was thought to be rather minor inflammatory lymphocytic infiltration and myelin phagocytosis. Barnett et al conclude that a novel process may be at work in acute MS lesions, whereby oligodendrocyte cell death precedes a secondary inflammatory reaction, and that current laboratory models of MS disease pathogenesis, particularly experimental allergic encephalomyelitis, are inadequate.

COMMENTARY

We know that MS is both clinically and pathological-

ly a heterogenous and complex disease, as recently characterized in a large autopsy and biopsy series of 73 MS cases by Lucchinetti and colleagues (Luchinetti C, et al. *Ann Neurol*. 2000;47:707-717). Indeed, other investigators have noted the presence of cell death markers on oligodendrocytes in MS, although without undergoing actual apoptosis (Bonetti B, CS Raine. *Ann Neurol*. 1997;42:74-84). Barnett and Prineas identified apoptotic cells by the finding of condensed nuclear chromatin, although other standard biomarkers such as tunnel staining or activated caspase-3 were not present. While the cell death pathways preceding apoptosis are unclear from this and other studies, Barnett and Prineas hypothesize that this initiates activated complement formation and subsequent leukocyte infiltration in MS lesions. The theory of T cell-mediated myelin destruction as the primary etiology in the immunopathogenesis of MS has yet to be satisfactorily established, and the above work raises a plausible scenario of tissue destruction that needs to be further addressed in future studies. — **BRIAN R. APATOFF**

Assessment of the Risk of Stroke or Blindness in Giant Cell Arteritis

ABSTRACT & COMMENTARY

Source: Nesher G, Berkun Y, Mates M, et al. Risk factors for cranial ischemic complications in giant cell arteritis. *Medicine.* 2004;83:114-122.

CENTRAL NERVOUS SYSTEM (CNS) ISCHEMIC complications including visual loss and stroke are the most dreaded manifestations of giant cell arteritis (GCA). Ischemic complications can be among the presenting manifestations of GCA or can develop at a later stage despite steroid treatment. The incidence of visual loss during the first year of steroid therapy has been reported to be as high as eight percent.[1] Similarly, stroke can occur soon after the beginning of steroid therapy. In one study,[2] 7 of 8 GCA patients with strokes were already receiving steroids, and the median interval between the start of steroid therapy and stroke onset was 10 days.

In order to identify risk factors for CNS ischemic complications at presentation and during follow-up, Nesher and associates reviewed the charts of 175 patients with GCA diagnosed between 1980 and 2000 at 4 Jerusalem hospitals. In 25% (n = 43) GCA presented with CNS complications. Thirty-two (18%) had acute loss of vision: 26 had anterior ischemic optic neuropathy (AION) and 6 had central retinal artery occlusion. Thirteen (7%) presented with strokes and 2 of them had a stroke and AION within 24 hours

Thirty-four percent of the patients with visual loss and 77% of the stroke patients had other GCA-related symptoms at the time of diagnosis. Transient ischemic attacks (TIA), visual or cerebral, were reported by 33 patients, half of whom (n = 17) eventually experienced persistent CNS ischemic complications. At presentation significant risk factors for CNS ischemic complications were TIA (odds ratio [OR], 4.3) and male sex (OR, 2.5). There was no significant association between CNS ischemic complications and the presence of diabetes, hypertension or hyperlipidemia, age, platelet count, hemoglobin level and ESR. The presence of systemic GCA-related symptoms (polymyalgia rheumatica, fever, fatigue, or anorexia) and the use of aspirin (100 mg/d) were associated with a lower risk (OR, 0.3).

Following the diagnosis of GCA and the initiation of steroid therapy, 14 of 166 patients (8%) developed CNS ischemic complications: 8 had vision loss and 6 had strokes. Risk factors in these patients were a previous CNS ischemic complication at presentation (OR, 5.6) and TIAs during followup (OR, 14.8). The use of low-dose aspirin was protective (OR, 0.2).

COMMENTARY

In agreement with other studies, Nesher and colleagues found that the presence of systemic symptoms was associated with a protective effect against CNS ischemic complications. The protective effect of fever was the most significant but its mechanism is unknown. There was no association between stroke or visual loss and jaw claudication or the results of standard laboratory tests of inflammation. The role of antiphospholipid antibodies and homocysteine in GCA-related CNS ischemia was not evaluated.

The good news from this study is that aspirin therapy during the follow-up period was protective.

Nesher et al have shown that GCA patients can be stratified into high- and low-risk groups for developing CNS ischemic complications. Future studies will be needed to determine whether high-risk patients might benefit from a more aggressive treatment approach including higher doses of steroids and possibly the addition of multiple antiplatelet agents. — **JOHN J. CARONNA**

References

1. Hoffman GS, et al. *Arthritis Rheum*. 2002;46: 1309-1318.

2. Gonzalez-Gay MA, et al. *Arthritis Rheum*. 1998;41:1497-1504.

Stroke During Cardiac Surgery: A Possible Opportunity for Prophylactic Neuroprotection?

ABSTRACT & COMMENTARY

Source: Stolz E, Gerrietz T, Kluge A et al. Diffusion-weighted magnetic resonance imaging and neurobiochemical markers after aortic valve replacement. Implications for future neuroprotective trials? *Stroke*. 2004;35:888-892.

CARDIAC SURGERY MAY BE COMPLICATED BY ischemic stroke as well as more non-specific cognitive disturbances. These events are largely attributed to the release of micro- and macro-embolic particles from complex atherosclerotic aortic arch disease. Diffusion-weighted MRI imaging may be effective in diagnosing these emboli not only when they are symptomatic, but also when they occur silently. Unless patients are scanned prospectively, however, the true incidence of these events is difficult to estimate. Even more importantly, the true clinical significance of these lesions is unclear. Could prophylactic neuroprotective strategies be employed in the setting? The data of Stolz and colleagues brings us one step closer to answering these questions.

A total of 45 consecutive patients underwent MRI scanning prior to and immediately following aortic valve replacement (AVR). Pre-existing T2 bright lesions were found in 26 patients. Postoperative diffusion-weighted infusion (DWI) lesions were found in 14 patients, 2 with territorial infarcts and the remainder with one or more punctate lesions. All patients were seen by a neurologist. Only 3 patients had a neurological deficit, 2 with territorial lesions and the third with a small white matter lesion. Measurements of S100B and neuron specific enolase (NSE), known markers of neuronal damage, were made sequentially. S100B values on days 2-4 postoperatively correlated with the presence of DWI lesions. In addition, DWI lesions were associated with increasing patient age and the presence of pre-existing T2 lesions on MRI. After additional analysis of these, only pre-existing T2 lesion volume was found to be a relevant predictor of DWI positivity. Stolz et al suggest that such T2 lesions may reflect prior microcirculatory damage and identify patients who are unable to optimally clear microembolic particles.

COMMENTARY

These data suggest that in the absence of a significant territorial infarct, DWI-positive lesions following cardiac surgery are largely asymptomatic and below the detection threshold of a detailed neurological examination. Such lesions may nevertheless be important and likely do contribute to long-term adverse neuro-psychiatric outcomes in these patients. The presence of pre-existing T2 lesions appears to be predictive of perioperative ischemic lesions and suggests that we may be able to preoperatively risk stratify patients undergoing cardiac surgery. While most patients may be able to clear microemboli easily, there may be a subset with an impaired microcirculation for whom these emboli present a much more serious problem. **— ALAN Z. SEGAL**

Gynecologists Beware

ABSTRACT & COMMENTARY

Source: Irvin W, et al. Minimizing the risk of neurologic injury in gynecologic surgery. *Obstet Gynecol*. 2004;103: 374-382.

NEW-ONSET LEG WEAKNESS OR NUMBNESS IS A common cause for neurologic consultation following gynecologic surgery. Usually such deficits are transient and do not necessitate extensive investigation. Infrequently, long-term disability results. This review addresses issues that would prevent such avoidable surgical complications.

Abdominal hysterectomy is the most common cause of iatrogenic femoral neuropathy. Stretch injury consequent to poor patient positioning or surgical dissection may be causative but, most often, prolonged compression by retractor blades is the cause. Self-retaining retractors appear particularly prone to cause this type of injury, consequent to ischemia resulting from pressure on the vaso nervorum. Recovery occurs anywhere from 3-65 days post-operatively but may be delayed even longer. When hand-held retractors are used, the incidence of femoral neuropathy drops from 7.5% to 0.7% following otherwise identical surgery. Thin patients, poorly developed rectus abdominis musculature, a narrow pelvis, prolonged surgery, and the extended Pfannenstiel incision (bikini line) all increase the risk of femoral neuropathy, and thus the choice of proper retractors in these populations is particularly warranted.

Meralgia paresthetica, consequent to intra-operative lateral femoral cutaneous nerve injury, shares the same etiologies as femoral neuropathy and may be similarly prevented. Genitofemoral neuropathy causes relatively mild sensory symptoms in the ipsilateral mons, labia majorum and femoral triangle and is most likely to occur during surgery for large pelvic sidewall masses or during external inguinal lymph node biopsy. Avoidance of injury can be achieved by identifying the nerve prior to excision of any mass.

Retroperitoneal surgery for malignancy or endometriosis most frequently injures the obturator nerve, resulting in thigh adduction weakness and upper medial thigh numbness. Again, adequate exposure of the nerve will best prevent this injury but may require retraction of the external iliac artery and vein. Sciatic neuropathy, a rare complication of laparotomy and usually due to the repair needed following unexpected pelvic hemorrhage, may similarly be avoided by diligent identification of the nerve before suture placement.

When a low transverse incision is used for pelvic surgery, the iliohypogastric and ilioinguinal nerve are most at risk due to their course between the internal and external oblique muscles in the anterior abdominal wall. Transection of the nerves may occur during the initial incision, they may be entrapped during suture placement, or a delayed-onset neuropathy may occur as a result of normal healing and scarring. Sharp/burning pain radiating from the incision site to the groin/symphysis (ilioinguinal) or mons/labia/upper inner thigh (iliohypogastric) region with paresthesia in the appropriate dermatome and relief after nerve block are the diagnostic triad for these entrapments. Coughing, sneezing, and stretching exacerbate the pain while bending at the knees provides temporary relief. Neurolysis is often necessary for cure. Not extending the surgical incision beyond the lateral border of the rectus sheath will significantly reduce the risk (3.7% following Pfannenstiel incisions) of this complication.

Vaginal surgery may similarly result in neurologic injury. Femoral neuropathy may occur bilaterally and is due not to compression from retractors but from prolonged incorrect lithotomy positioning. Excessive hip flexion, abduction, and external hip rotation allows the femoral nerve to be compressed under the inguinal ligament. Should prolonged surgery be necessary, periodic repositioning is advisable.

Sciatic nerve injury occurs in 0.3% following vaginal hysterectomy and is a result of stretch injury due to its being fixed at the sciatic notch and fibular head, not allowing significant "give." Moderate hip flexion and thigh abduction with minimal hip external rotation is the optimal lithotomy position to prevent this injury.

Postoperative gluteal pain and perineal anesthesia from pudendal neuropathy may occur if the nerve is inadvertently incorporated into a suture line. Reexploration is often necessary to provide relief by releasing the entrapped nerve.

Neurologic injury following gynecologic surgery cannot be eliminated, but its incidence may be decreased by careful patient positioning, careful placement of retractor blades, limiting excisions where possible, and obtaining adequate exposure of the surgical field.

COMMENTARY

Neurologic injury following obstetrical labor and delivery occurs infrequently. Among 6048 women who delivered a live-born child between July 1997 and June 1998, 56 (0.92%) experienced a new nerve injury confirmed by examination (Wong CA, et al. *Obstet Gynecol*. 2003;101:279-288). Most commonly, mononeuropathy of the lateral femoral cutaneous (n = 24) or femoral (n = 22) nerve was seen, followed by L4, L5, or S1 radiculopathy (n = 5), obturator, common peroneal or lumbosacral plexopathy (n = 3 each), and sciatic neuropathy (n = 2). Recovery occurred in a median of 2 months but ranged from 1 week to more than 18 months. Nulliparity and protracted second stage of labor with prolonged pushing in the semi-Fowler-lithotomy position were found, by logistic regression analysis, to be associated with nerve injury. Regional anesthesia, assisted vaginal delivery, newborn weight, pre-pregnancy basal metabolic index, fetal presentation (cephalad or otherwise), gestational period, and weight gain were not significant risk factors for injury. **— MICHAEL RUBIN**

Is Neuroimaging Needed to Assess Acute Oculomotor Nerve Palsies?

ABSTRACT & COMMENTARY

Source: Chou KL, et al. Acute ocular motor mononeuropathies: Prospective study of the roles of neuroimaging and clinical assessment. *J Neurol Sci*. 2004;2129:35-39.

This paper reports the results of a prospective study of patients aged 50 years and older with acute isolated third, fourth, and sixth nerve palsies. The need for immediate neuroimaging in these patients was evaluated. Chou and colleagues prospectively evaluated 66 patients. They attempted to determine the need for neu-

roimaging as well as the role of clinical assessment in determining etiology. They investigated the rapidity of onset of the cranial nerve palsies. They found that the time to maximal diplopic symptoms was not predictive of etiology and that there was a median of 2 days for both peripheral microvascular and other etiologies. The presence of peripheral vascular risk factors such as diabetes mellitus, hypertension, hypercholesterolemia, and coronary artery disease was significantly associated with a microvascular etiology. Despite this, other causes were identified by magnetic resonance imaging or computed tomography scanning in 14% of the patients. These results suggest that neuroimaging may have a role in the initial evaluation of patients with acute ocular mononeuropathies regardless of age.

COMMENTARY

Isolated third, fourth and sixth nerve palsies are a common cause of acute diplopia in neurological practice. The most common etiology is microvascular ischemia of the peripheral portion of the nerves. Microvascular ocular motor nerve ischemia is a presumptive diagnosis in the absence of other neurological signs or symptoms, when no new findings occur during the follow-up period and with spontaneous complete recovery usually within 4 months. It has been controversial whether these patients needed neuroimaging particularly in patients older than age 50. It is widely accepted that acute ocular motor mononeuropathies in persons younger than 50 years of age should be assessed using neuroradiological methods. In the present study, etiologies in 9 patients of 66 who had lesions other than peripheral microvascular ischemia included intracranial neoplasm, brain stem infarct, aneurysm (which was in 1 patient—a pupil sparing third nerve palsy), demyelinating disease, and pituitary apoplexy. The management of these patients would have been delayed if the underlying etiology had not been determined using neuroradiological imaging.

The present investigation also shows that historical data, including the time to maximal diplopic symptoms and vascular risk factors, could not be used with complete confidence to distinguish peripheral microvascular from other etiologies.

It is generally accepted that third nerve palsies, which accompany diabetes, spare the pupil. However, in the present study, microvascular third nerve palsies showed pupillary involvement in 28% of cases, and in 43% of the cases the anisocoria was more than 2 mm. Chou et al note that the 14% of patients who had etiologies other than microvascular would have had an alteration in immediate patient management. They, therefore, recommend neuroimaging in the initial evaluation of adults with acute ocular motor mononeuropathies. This appears to be a reasonable recommendation.

— M. FLINT BEAL

Do Seizures in Older Adults Predict Stroke Risk?

ABSTRACTS & COMMENTARY

Sources: Cleary P, et al. Late-onset seizures as a predictor of subsequent stroke. *Lancet.* 2004;363:1184-86; Sudlow, CM. Epilepsy and stroke (commentary). *Lancet*. 2004;363: 1175-1176.

USING DATA FROM THE UK GENERAL PRACTICE Research Database (GPRD), Cleary and associates evaluated the hypothesis that late-onset (60-year-old subjects and older) seizures increase the risk of subsequent stroke. The 4709 subjects (with no prior history of cerebrovascular disease, other brain injury, brain tumor, alcohol, or drug abuse, or dementia) were compared to 4709 age- and gender-matched seizure-free individuals from the same database. There was a highly significant ($P < 0.0001$) difference in subsequent stroke-free survival in seizure patients vs controls. By Cox's model, the relative risk of stroke was 2.89 (95% confidence interval, 2.45-3.41).

In an accompanying editorial, Sudlow suggests that "it seems reasonable for general practitioners, general physicians, geriatricians, and neurologists . . . to assess their patients' vascular risk factors, and to consider treatment to prevent stroke (and other vascular disease)."

COMMENTARY

There are limitations to the present study, which go to the heart of the association of new-onset seizures and subsequent stroke risk. The main question is whether seizures are a true marker for stroke or an epiphenomenon. Seizures in older adults are more likely to be symptomatic than in younger individuals, with idiopathic and cryptogenic epilepsy being more common in the latter. We suspect that the GPRD does not capture important data to solidify the claim that seizures are an independent predictor of stroke risk. First, while a prior history of cerebrovascular disease was an exclusion criterion for the study group, there is no indication whether this exclusion was rigorously defined by neuroimaging in addition to clinical history and examination. Second, it is unlikely that the evaluation of the patients' new-onset seizures included diffusion-weighted

imaging (to exclude ischemic stroke) or echo gradient MRI sequences (to exclude subtle focal cortical hemorrhage). Without these data, one is left to wonder whether many late-onset seizures are due to existing cerebrovascular disease. If so the conclusion of the study is not particularly novel: previous stroke predicts subsequent stroke.

Even if seizures in older individuals are not an independent marker of cerebrovascular disease, we agree with the investigators that these seizures should be a red flag to consider treatment to modify stroke risk (be it primary or secondary prevention). — **ANDY DEAN**

CME Questions

20. Choose the true statement:

a. Prednisone, administered early in the course of ocular myasthenia, appears to affect its progression to generalized disease
b. Seronegative myasthenia gravis patients do not benefit from thymectomy as much as do seropositive patients
c. A higher frequency of thymoma occurs in seronegative myasthenia gravis patients compared to seropositive myasthenia gravis patients
d. Speech pathology evaluation is an excellent way of predicting the risk of aspiration in myasthenia gravis patients at the bedside
e. All the above are true or false

21. During steroid treatment, which of the following is/are risk factors for GCA-related stroke or vision loss?

a. fever
b. jaw claudication
c. diabetes mellitus
d. previous stroke or visual loss
e. ue of low-dose aspirin.

22. **Risk factors for iatrogenic femoral neuropathy following abdominal hysterectomy include:**

a. poorly developed rectus abdominis musculature
b. a narrow pelvis
c. prolonged surgery
d. the extended Pfannenstiel incision ("bikini line")
e. All of the above

23. The following have shown to be successful targets in the treatment of migraine except:

a. dopamine receptors
b. 5-HT2 receptors
c. 5-HT 1B/ 1D receptors
d. CGRP receptors
e. nitric oxide synthetase.

Answers: 20 (a); 21 (d); 22 (e); 23 (e)

In Future Issues:

A Polymorphism in the Cyclooxygenase 2 Gene as an Inherited Protective Factor Against Myocardial Infarction and Stroke