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INSIDE

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Statin Withdrawal May Lead to Adverse Outcomes in Acute Stroke

ABSTRACT & COMMENTARY

By Alan Z. Segal, MD
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Dr. Segal is on the speaker's bureau for Boehringer-Ingelheim.

Synopsis: Withdrawal of statin therapy in acute ischemic stroke may lead to increases in death and disability.

Sources: Colivicchi F, et al. Discontinuation of statin therapy and clinical outcome after ischemic stroke. Stroke 2007; 38: Online, August 30, 2007. Blanco M et al. Statin treatment withdrawal in ischemic stroke. *Neurology* 2007; 69: 904-910.

STATIN THERAPY HAS A WELL-RECOGNIZED ROLE IN THE primary and secondary prevention of stroke. Statins may also have a neuroprotective effect in the setting of acute stroke. This has been well documented in animal models and high dose acute statin therapy is currently under investigation in human subjects. Pretreatment with statins is also likely to have benefit. Discontinuation of statins in the acute setting may precipitate vascular dysfunction and exacerbate ischemic events including both stroke and myocardial infarction.

In a single center study in Spain, Blanco and colleagues studied 215 patients with acute ischemic stroke, 89 of whom were previously taking statin medications. These patients were randomly assigned to have statin therapy withheld for three days (statin withdrawal group) or to be treated with 20 mg atorvastatin either orally or via nasogastric tube (statin treated group). All patients were treated with statins starting on day 4, including the 126 remaining patients who had not previously been treated with statin therapy (reference group).

At 3 months, 60% of patients in the statin withdrawal group met the primary outcome variable of death or dependence compared with 39% in the statin treated group. The adjusted odds ratio favoring a poor outcome among statin withdrawal patients was 2.39, increasing to 4.66 (1.46 - 14.91) after adjustment for age and stroke severity. Early neurological deterioration, defined as an increase of ≥ 4 points on the NIHSS, was observed in 65% of statin withdrawal patients compared with 21% of statin treated patients. Infarct volume was

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also greater in the statin withdrawal group, with a mean increase of 37 mL compared with treated patients. In post-hoc analyses, statin withdrawal patients also fared more poorly than patients in the reference group with regard to all endpoints-death and dependency, early neurological deterioration and infarct volume.

In a related study, Colivicchi and colleagues studied 631 patients with an ischemic stroke and followed them for one year to assess their adherence to statin therapy. Among 409 patients who received artorvastatin therapy, 163 discontinued this medication and among 222 patients who received simvastatin, 83 had stopped taking this at one year. Among the 631 patients, 116 (18%) died during one-year follow up. After adjusting for confounding variables, including stroke severity, discontinuation of statin was an independent predictor of mortality with a hazard ratio of 2.78. This effect was more pronounced with early discontinuation, leveling off in the 9-12 month interval. Discontinuation of anti-platelet therapy was also an independent predictor of death, though with a less profound effect (hazard ratio of 1.81).

Statin therapy was discontinued due to side effects (most commonly dyspepsia) in a minority of patients (29%) and was unexplained in the remaining 71%. Patients who discontinued statins were older and more commonly female. Statins were more likely to be continued among patients who were diabetic or who had a history of previous stroke.

COMMENTARY

As Blanco indicates, animal as well as human data strongly suggest that withdrawal of statin therapy in an acute stroke patient may impair vascular function and trigger a dangerous inflammatory and prothrombotic state. This raises a major red flag in our treatment of acutely hospitalized stroke patients. Patients on previous statin therapy who have the medication discontinued face a 4.7 fold increase in their risk of death or dependency due to their stroke. This effect is even more pronounced than among patients not previously receiving statin medications.

These data raise important practical implications regarding the "nuts and bolts" of emergency room and immediate hospital care for acute stroke patients. Patients with severe strokes, who cannot take oral medications due to dysphagia, must receive these via nasogastric tube. Such patients are commonly made NPO, with feeding and oral medication administration delayed until their swallow status can be clarified. These issues are particularly germane to patients receiving thrombolysis. Among patients receiving intravenous tPA, our protocol mandates placement of a Foley catheter prior to thrombolysis since such an invasive procedure cannot be performed once tPA has been administered. The same would likely apply to a nasogastric tube.

The data of Colivicchi are more difficult to understand. Discontinuation of statin therapy was highly associated with post-stroke mortality, but it is not clear if this was a cause, or more likely merely an effect of practice patterns among patients with more devastating strokes. It is testament to the inconclusive nature of this study that the justification for cessation of statin therapy was unexplained in over 70% of patients. In addition, while over 80% of the deaths were attributed to cardiovascular causes, data such as this, gleaned from death certificates, is unlikely to reflect the true etiology of their demise. Notably, recurrent stroke was not documented as the cause of death among any of the patients from whom statins were withdrawn. ■

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Dementia with Lewy Bodies vs Parkinson's Disease with Dementia: Different Patterns of Cortical Atrophy

ABSTRACT & COMMENTARY

By Melissa J. Nirenberg, MD, PhD
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Dr. Nirenberg does research for Boehringer-Ingelheim.

Synopsis: Dementia with Lewy bodies is associated with greater temporal, parietal, and occipital lobe atrophy than Parkinson's disease with dementia.

Source: Beyer, MK et al. Gray matter atrophy in Parkinson disease with dementia and dementia with Lewy bodies, *Neurology* 2007; 69(8):747-754.

THE COMBINATION OF DEMENTIA, PARKINSONISM, and Lewy body pathology occurs in both dementia with Lewy bodies (DLB) and Parkinson disease with dementia (PDD). Postmortem studies of DLB and PDD have shown widely distributed Lewy bodies, with no clear-cut pathological distinction between the two. DLB and PDD are therefore defined by consensus clinical criteria, with the onset of dementia within the first year of disease in DLB, and after at least a year of parkinsonism in PDD. Although this distinction is somewhat arbitrary, it is clinically useful for estimating prognosis and predicting responsiveness to dopaminergic medications.

In this study, the authors used MRI voxel-based morphometry (VBM) to evaluate and compare the patterns of cortical atrophy in patients who met consensus clinical criteria for DLB (n = 18), PDD (n = 15), or Alzheimer's disease (AD) (n = 21), versus healthy, elderly control subjects (n = 20). The baseline characteristics of these groups differed in several respects, with a significantly higher mean age of subjects in the DLB than the PDD or control groups, and a significantly longer duration of dementia in the DLB and AD than in the PDD group. The groups also differed in educational background, gender distribution, and current medications. Mini-mental State Examination scores were comparable in the 3 disease groups, and lower than those of control subjects.

The major finding of the study was the presence of significantly greater gray matter atrophy in the temporal, parietal, and occipital lobes in DLB than in PDD, even after statistical adjustment for age. As expected, there was also significantly greater cortical atrophy in AD than either DLB or PDD, particularly in the medial temporal lobes. All subjects with dementia (DLB, PDD, or AD) exhibited diffuse gray matter atrophy compared with healthy, non-demented controls. The results suggest that PDD and DLB can be distinguished by differences in cortical gray matter atrophy.

COMMENTARY

Most neurodegenerative disorders have characteristic neuropathological findings that allow for a definitive postmortem diagnosis, which can be used as a "gold standard" against which the sensitivity and specificity of clinical diagnostic criteria or biomarkers can be evaluated. DLB and PDD, however, cannot be distinguished on this basis. This highlights the need for biomarkers to distinguish between DLB and PDD, and calls into question whether they are distinct entities or part of a spectrum of Lewy body dementias.

This study provides new evidence that there may be greater temporal, parietal, and occipital lobe atrophy in DLB than PDD, providing an anatomical substrate for observed clinical differences between the two disorders, and supporting the hypothesis that they are distinct nosological entities. Limitations include the relatively small sample size, potential confounders (due to baseline differences between the study groups), and lack of neuropathological diagnosis. The findings contradict those of a prior VBM study in which no significant differences between DLB and PDD were observed. Future studies with larger sample sizes, more closely matched subjects, and neuropathological correlation would be helpful to confirm and expand the findings of the current study. Given the wide range of normal anatomical variation, VBM may eventually be useful for distinguishing DLB from PDD on a population basis, but is unlikely to facilitate diagnosis within individual patients. ■

Additional Reading:

Seppi O and Rascol O. Dementia with Lewy bodies and Parkinson disease with dementia: Can MRI make the difference? *Neurology* 2007; 69(8):717-718.

Telemedicine for Stroke: An Idea Whose Time Has Come

ABSTRACT AND 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: Outcomes for treatment of stroke with intravenous tissue plasminogen activator (tPA) were similar at community hospitals supported by telemedicine consultation with stroke experts compared to academic stroke centers.

Source: Schwab, S et al. on behalf of the TEMPiS Group. Long-Term Outcome After Thrombolysis in Telemedical Stroke Care. *Neurology* 2007;69:898.

ALTHOUGH INTRAVENOUS RECOMBINANT TISSUE plasminogen activator (tPA) is the only FDA

approved treatment for acute ischemic stroke, it is still given to only 1 to 6% of stroke patients. Many patients are not eligible for IV tPA because they arrive at a hospital after the 3-hour window, but there are many small hospitals where tPA is not routinely given because there is insufficient expertise in the use of this beneficial medicine, which also has a significant risk of catastrophic bleeding.

Several studies have suggested that it is feasible to safely administer tPA when stroke experts at a remote center consult through the use of high-speed data transmission that permits experts to view imaging studies and to examine patients by live audiovisual conferencing. In a previous study, the TEMPiS investigators demonstrated that in the first year of their stroke telemedicine project, the number of tPA patients treated in the 12 participating community hospitals increased from a total of 10 patients annually to 110 patients (4.4% of the total number of ischemic strokes). These investigators have now directly compared patients treated with telemedical consultation to patients treated at the academic stroke centers where the experts work.

The investigators established a network of 12 community hospitals in Germany, supported by experts from 2 regional stroke centers. The stroke centers provided teleconferencing starting within 3 minutes of a request. Images were transferred and reviewed; a videoconference link was then established so that the expert could examine the patient with the help of a local physician.

During the first 22 months of the project, 170 patients received IV tPA at the community hospitals after telemedical consultation, and 132 were treated at the stroke centers. The baseline characteristics of the patients were similar with a median admission NIH stroke score of 12 in the telemedical group and 11 in the stroke center group. The authors found no statistically significant differences in outcome between the two groups. 39.5% of the telemedicine group had a modified Rankin score (mRS) of 0 or 1 (no symptoms or minimal disability) compared to 30.9% of the stroke center patients at 6 months. Mortality at 6 months was 14.2% in the telemedicine group and 13.0% in the stroke center group. The results in both groups compare favorably to the mortality rate of 21% at 6 months in the NIH trial that led to the approval of tPA.

In making plans to establish other telemedicine networks for stroke care, one other important point should be noted about the TEMPiS project. It not only provided initial telemedicine consultations to the community hospitals, but also established local stroke units and stroke teams and guaranteed availability of CT scanning 24 hours per day, along with neurovascular ultrasound. All of these measures may have contributed to the results seen in the community hospitals. Telemedicine, in conjunction with appropriate care after the first three hours, appears to be a safe and effective way of making the benefits of tPA available to more patients. ■

"Peroneal Tunnel" Neuropathy?

ABSTRACT & COMMENTARY

By Michael Rubin, MD

Professor of Clinical Neurology, NewYork-Presbyterian Hospital, Weill Cornell Medical Center

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

Synopsis: Idiopathic peroneal neuropathy may be associated with entrapment in a tunnel formed by the short head of the biceps femoris muscle.

Source: Vieira RLR, Rosenberg ZS, Kiprovski K. MRI of the distal biceps femoris muscle: normal anatomy, variants, and association with common peroneal entrapment neuropathy. *AJR* 2007;189: 549-555.

For many patients with common peroneal neuropathy, the most common entrapment neuropathy in the leg, no specific cause can be found. Anatomic variability, hitherto undescribed, of the distal biceps femoris muscle may be the underlying cause in some of these idiopathic cases. In this study, 100 consecutive 1.5-T magnetic resonance (MR) examinations of the knee were reviewed by 2 musculoskeletal radiologists, to determine the normal anatomy of the region, any anatomic variation of the biceps femoris muscle, and the relationship of the common peroneal nerve to the muscle. Patients were excluded if there was evidence for signal abnormality or deformity of the posterolateral knee, including the joint capsule and ligaments, or any history of peroneal neuropathy. MR slice thickness was 4 mm, and MR protocol incorporated axial T1 and T2 fat-saturated, coronal proton density and T2 fat-saturated, and sagittal proton density and proton density fat-saturated images. Parameters recorded included the presence of any denervation edema in muscle, any signal abnormality of the common peroneal nerve, and any variation of the distal biceps femoris muscle. Statistical analysis was performed using the Mann-Whitney test.

In 77 % (n = 77), abundant fat posterior to the short head of the biceps femoris and superficial to the lateral head of the gastrocnemius surrounded the common peroneal nerve. In the remaining 23% (n = 23), the lateral head of the gastrocnemius and the short head of the

biceps femoris surrounded a narrow tunnel, averaging 2.4 cm in length (range 1.5 - 4.0 cm), which was relatively fat free. The presence of this tunnel was significantly predicted by a closer distance between the joint capsule and short head of the biceps femoris (mean 0.05 cm vs 0.6 cm, $P < 0.001$), and longer posterior extent of the short head of the biceps femoris muscle at the level of the femoral condyles (mean 1.50 cm vs 1.02 cm, $P = 0.005$). No patient had an accessory biceps femoris tendon. This tunnel is newly described and has not previously been referred to as a cause of peroneal neuropathy. Its relative lack of fat offers a possible relationship between the 2.

COMMENTARY

Among 67 consecutive patients with peroneal mononeuropathy enrolled in an Italian multi-center study from November 2002 to January 2004, 16% remained idiopathic despite intensive investigation (*JPNS* 2005;10:259-268). Overall, men outnumbered women by a 4:1 ratio, mean age was 47.9 years, 97% were unilateral, and the common peroneal nerve was involved in 89.9%, compared to 8.7% and 1.4% affecting the deep or superficial branch, respectively. Sensory deficits were found in 87.9%, accompanied by pain in 19.7%. Causes included prolonged compression due to awkward posture (23.1%), surgery, including hip replacement, tibial osteotomy, thoracic, abdominal, thyroid, and prostate surgery (20.3%), weight loss (14.5%), trauma (11.6%), prolonged bed confinement (7.3%), compression from casting (5.8%), and arthrogenic fibular cyst (1.4%). Perioperative and idiopathic peroneal neuropathy were equally likely to be either axonal or demyelinating in nature, whereas trauma caused exclusively axonal injury in 60%. Older patients (> 60 years) experienced greater disability and pain, and longer duration correlated with greater disability. Those with idiopathic peroneal mononeuropathy tended to have a better quality of life.

What Causes Cognitive Impairment After Coronary Bypass Surgery?

ABSTRACT & COMMENTARY

By Matthew E. Fink, MD

Synopsis: A large difference between preoperative blood pressure and intraoperative perfusion pressure increases the risk of postoperative cognitive impairment and stroke.

Source: Gottesman RF, Hillis AE, Graga MA, et. al. Early postoperative cognitive dysfunction and blood pressure during coronary artery bypass graft operation. *Arch Neurol* 2007; 64: 1111-1114.

NEUROLOGICAL IMPAIRMENT IS THE MOST FEARED complication of cardiac surgery, and great efforts have been made to reduce this complication. Stroke is reported in < 1% of low risk patients, but risk increases with increasing age, prior stroke or TIA, presence of carotid or vertebral artery stenosis, or the presence of hypertension and diabetes. Early cognitive impairment has been reported to occur in as many as 60% of patients, but the vast majority recover without long-term sequelae.

What causes these complications and how can they be prevented? The study by Gottesman and colleagues, from Johns Hopkins Hospital, sheds light on a possible mechanism for brain ischemia during heart surgery - a differential between preoperative blood pressure and cardiopulmonary pump pressure during surgery.

Gottesman et al. prospectively studied 15 patients who had on-pump coronary artery bypass surgery and measured Mini-Mental State Examination (MMSE), Trails A and B, and the Rankin score, before and after surgery, and correlated changes in these measures with changes from preoperative mean blood pressure to mean cardiopulmonary bypass pump perfusion pressure. They found a significant correlation between change in MMSE and the magnitude of BP change in the early postoperative period. A drop in mean arterial pressure predicted a decline in the MMSE, and the greater the preoperative mean arterial blood pressure, the greater the decline in MMSE. At one month postoperatively, most patients had recovered, but the few who had BP drops of >27 mm Hg had persistent declines in MMSE scores. None of the other measures had significant differences.

In addition, 13 patients had postoperative brain MRI studies, and 6 were found to have at least one DWI positive lesion. There was a trend that suggested a higher risk of brain lesions for patients with the largest drops in blood pressure, but the small number of patients did not allow for valid statistical analysis.

COMMENTARY

Microemboli from the aortic arch as well as intracardiac air and particle emboli have been implicated as a cause of intraoperative stroke, but mechanical improvements in bypass techniques have reduced these risks. Blood flow alterations during cardiopulmonary bypass have been postulated as a cause of brain ischemia, but studies comparing "off-pump" surgery to cardiopulmonary bypass have shown no difference in stroke rate between the 2 groups (*N Eng J Med* 2003;348:394-402).

The report by Gottesman et al points to a preventable mechanism, a drop in blood pressure during bypass, that can be ameliorated. Efforts should be made to reduce and stabilize the patient's blood pressure before surgery, and maintain maximum tolerable pressure during bypass, to avoid brain ischemia. ■

On the Origin of PLEDs: Are Cortical and Subcortical PLEDs Electrographically Different?

ABSTRACT & COMMENTARY

By Padmaja Kandula, MD
Assistant Professor of Neurology and Neuroscience, Comprehensive Epilepsy Center, Weill Medical College of Cornell University.

Dr. Kandula reports no financial relationships relevant to this field of study.

Synopsis: This retrospective study correlates neuroimaging lesion distribution with periodic lateralized epileptiform discharges (PLEDS) and points out the different characteristics of PLEDS from cortical vs. subcortical origin.

Sources: Kalamangalam GP, et al; Neuroimaging and neurophysiology of periodic lateralized epileptiform discharges: observations and hypotheses. *Epilepsia*. 2007; 48(7):1396-1405.

THE OCCURRENCE OF PLEDS DURING A ROUTINE electroencephalographic study is not a new concept. In fact, the relevance of this elusive discharge has been the focus of interest over the last 2 decades, particularly since the advent of higher resolution imaging techniques. This recent retrospective study performed at the Cleveland Clinic aims to answer whether PLED morphology has any association with lesion location.

Over a 4-year period, 106 patients with PLEDs were retrospectively identified from an EEG database. These 106 patients were then classified into one of 5 groups based upon corresponding imaging (CT and/or MRI) characteristics: normal, acute cortical, acute subcortical, chronic cortical, and chronic subcortical. Classification of imaging abnormalities prioritized acute over chronic changes, and cortical over subcortical changes. This stratification of data based on neuroimaging constituted part I of the study.

In part II of the study, raw EEG data was scored quantitatively and/or qualitatively by a senior epileptologist, blinded to the neuroimaging findings in 95/106 patients where the original, complete EEG record was available. The selected 30 seconds of artifact free EEG was then scored, based on the following characteristics: inter-PLED interval (repetition rate), duration of complex, amplitude, prominent polarity, morphology (number of sharp phases and total number of phases), distribution, degree of intervening slow rhythms (subjective estimate) and reactivity. Of the 95 patients, 35 patient EEG records were excluded due to greater than one independent PLED population (eg. BIPLED), unsustained PLEDS (< 20 seconds during the recording), and physician disagreement with the original EEG classification. EEGs associated with normal neuroimaging were also excluded. Of the remaining 60 records, 49 of the records were associated with a cortical lesion (group A) and 11 records with a subcortical lesion (group B).

The results of part I of the study showed that acute cortical lesions were the most common abnormality (40.5%). However, subcortical lesions (both acute and chronic combined) were not infrequent (23.6%).

In part II of the study, the electrographic characteristics of group A (cortical) and group B(subcortical) were compared. Overall, the duration of a typical cortical PLED (sharp or spike-and-slow wave discharge) was longer (mean 574 msec) than a subcortical one (mean 420 msec). Cortical PLEDSs were also more variable in morphology (mean of 2.367 in group A vs. mean of 1.727 in group B). However, repetition rate and degree of intervening background slowing between successive PLEDs was not statistically significant between the 2 groups.

COMMENTARY

Over the years, much debate has ensued regarding the neuroanatomic and pathophysiologic aspects of this periodic entity. Although retrospective in nature, this study is one of few that correlates electrographic activity with neuroimaging. Clinically, the appearance of PLEDs in instances of cortical lesions is not surprising, as epileptiform discharges in general are thought to arise from cortical gray matter. However, the fairly high frequency of both acute and chronic subcortical PLEDs in this study is surprising and interesting.

Inherent drawbacks to this study are classification of the imaging abnormalities, where cortical or subcortical reflected the location of the predominant imaging abnormality as regarded by the senior author. In reality, most lesions involve both subcortical and cortical structures, making definitive stratification difficult. Also, the proportion of lesion type may have been influenced by lack of MRI confirmation (only CT evidence) of lesions in one third of patients. The retrospective nature of the study also limited the number of full EEG recordings available for review.

The authors present a unifying theory of PLED gene-

sis where discharges can arise from perturbation of a segment(s) of the interconnected cortical-subcortical circuit. The electroencephalographic "signature" or synchronous oscillations seen on scalp EEG may reflect the spatial origin of PLEDs. This theory seems plausible as established animal models for sleep neurophysiology have shown reproducible 12-14 Hz rhythms (sleep spindles) originating from reticular-thalamocortical connections. The authors further speculate that subcortical PLEDs are relatively shorter duration and stereotyped due to the restricted extent of the lesion and rapidly conducting white matter projections, in comparison to cortical PLEDs. Although the number of subcortical PLEDs (n = 11) analyzed in this study were small, the finding of shorter duration and stereotypical morphology of subcortical vs cortical PLEDs supports the above hypothesis.

This paper and other recent papers (Gurer et al, *Clin EEG* 2004;35:88-93 and Gross et al, EEG C*lin Neurophysiol* 1998;107:434-438) support the idea of subcortical PLEDs, challenging the classical notion that PLEDs are only a manifestation of acute cortical lesions. However, further, large-scale prospective studies, with concomitant EEG and adjunctive neurophysiologic monitoring, such as magnetoencephalographic analysis, may help shed further light on the origin of periodic patterns such as PLEDs. ■

Young Woman — Do Not Visualize Your Migraine Aura Through Cigarette Smoke!

ABSTRACT & COMMENTARY

By Dara G. Jamieson, MD
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Weill Medical College, Cornell University
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Synopsis: Young women with recent probable migraine with visual aura are at increased risk of ischemic stroke, especially if they both smoke and use oral contraceptives. Even though their absolute risk of stroke is low, these patients should be encouraged to stop smoking.

Sources: MacClellan LR, Giles W, Cole J, Wozniak M, Stern B, Mitchell BD, Kittner S. Probable migraine with visual aura and risk of ischemic stroke: The Stroke Prevention in Young Women Study. *Stroke* 2007; 38:2438-2445.
Kurth T. Migraine with aura and ischemic stroke. Which additional factors matter? *Stroke* 2007;38:2407-2408.

THE ASSOCIATION BETWEEN MIGRAINE AND ischemic stroke has been noted in multiple clinical trials of both men and women. The correlation seems greatest in young women with migraine with aura, as noted in the Women's Health Study (WHS) (Kurth *JAMA* 2006). The confounding effect of patent foramen ovale (PFO), a risk factor for ischemic stroke in young people that is present in approximately half of all migraineurs with aura, is unclear. The additional risk conferred by other factors, such as hypertension, diabetes, smoking, and oral contraceptive use, awaits elucidation.

The Stroke Prevention in Young Women Study (SPYW) is a population-based, case-control study initiated to examine risk factors for ischemic stroke in young women. Case data from women aged 15 to 49 years, who were hospitalized with a first ischemic stroke in hospitals in the Greater Baltimore-Washington area, was accumulated between 1992 and 1996 and between 2001 and 2003. Age and geographically matched control subjects were recruited by random digit dialing. The presence of symptoms of migraine headaches was assessed retrospectively in the controls and the stroke cases. The symptom criteria in the questionnaire used to define the headaches was less specific than the International Headache Society (IHS) criteria, without reference to phonophobia, duration of the migraine, or timing of the aura. Because the migraine diagnosis did not strictly adhere to the IHS diagnostic criteria for migraine, the headaches in the SPYW were called probable migraine with or without aura. The duration of exposure to probable migraine was divided into first probable migraine either within one year, within 1 to 12 years, and greater than 12 years before ischemic stroke onset. Probable migraine frequency and severity were assessed by patient interview. Traditional stroke risk factors, demographic characteristics and history of probable migraine were assessed in 386 young women who had a stroke and 614 non-stroke controls. Clinical and neuroimaging data was used to classify location of the stroke. Statistical analysis compared risk factor distribution between cases and controls.

The women in the study with a stroke were older on average and more likely to be African-American. Cases were more likely than controls to report a history of traditional risk factors such as hypertension, diabetes, and myocardial infarction and were more likely to be current smokers and current oral contraceptive users. Stroke patients reported a statistically significant increase in history of probable migraine with visual aura (PMVA), as compared to controls. But, there was no significant difference in history of probable migraine without aura between stroke cases and controls. PMVA was a significant risk factor for stroke among women without tradi-

tional vascular risk factors, as compared to either nonmigraineurs or women with migraine without aura. PMVA was a significant risk factor for stroke among smokers (odds ratio 1.5; 95% CI, 1.1 to 2.3) with an increased risk in migraineurs with aura who smoked and who also use oral contraceptives. Women with PMVA who smoked and used oral contraceptives had increased stroke risk as compared to either women with PMVA (7.0 OR; 95% CI, 1.4 to 22.8) or nonmigraineurs (10.0 OR; 95% CI, 1.4 to 73.7) who were nonsmokers and did not use oral contraceptives. The vascular risk increased with chronological proximity between the woman's first episode of PMVA and the time of her stroke. There was no correlation between probable migraine and stroke location. The study did not show an association between migraine with aura, ischemic stroke risk and PFO, but echocardiography with air contrast was performed in only 163 stroke patients.

COMMENTARY

The SPYW, a population-based, case-control study of young women with stroke, found that PMVA was associated with an increased risk of ischemic stroke, particularly stroke of undetermined origin. The risk of ischemic stroke associated with recent PMVA, which was independent of a history of hypertension, diabetes, and myocardial infarction, correlated with the findings of other studies of women with migraine including the WHS. The presence of a PFO has been implicated in the association between migraine with aura and ischemic stroke in young women, but this does not explain the increased risk of myocardial infarction in women with migraine with aura noted in WHS. While neither smoking nor oral contraceptive use independently modified the effect of PMVA on stroke risk in the SPYW, these 2 factors had a multiplicative effect on the risk of stroke.

The article was published with an editorial by Tobias Kurth, MD, ScD, who emphasized that, despite the results of the SPYW and other studies linking migraine with aura and ischemic stroke, the risk of stroke for these women is still very small. He noted methodological considerations in the SPYW: the prevalence of PMVA was high among the controls (29%) with potential underestimation of effect, and the retrospective information about migraines was ascertained after the stroke, with potential recall bias or linkage between the 2 events. However, consistent evidence that smoking substantially increases the risk of ischemic stroke in young women with migraine with aura reiterates the need to continue to encourage smoking cessation in migraineurs, especially those women whose headache is associated with an aura.

Additional Reading:

Kurth T, Gaziano JM, Cook NR, Logroscino G, Diener H-C, Bering JE. Migraine and risk of cardiovascular disease in women *JAMA* 2006; 296:283-291.

CME Questions

8. Compared with Parkinson disease dementia, diffuse Lewy body disease was associated with greater atrophy all of the following regions EXCEPT:

a. Frontal lobe
b. Parietal lobe
c. Temporal lobe
d. Occipital lobe

9. What percentage of stroke patients treated with IV TPA after telemedicine consultation had minimal or no disability at 6 months?

a. 6.5%
b. 24%
c. 39.5%
d. 81.2%

10. Peroneal neuropathy

a. Is most often idiopathic
b. Usually involves the deep peroneal branch exclusively
c. Is most often axonal in nature
d. Is more often seen in men than in women
e. None or all the above are true

11. Women with probable migraine with aura:

a. have the same vascular risk as women without aura
b. have an increased stroke risk associated with a history of diabetes.
c. have an increased stroke risk only if they also have a PFO.
d. have the greatest risk of stroke if they smoke, while taking oral contraceptives.
e. have about a two-fold increased risk of stroke if they smoke and use oral contraceptives.

Answers: 8.(a) 9.(c) 10.(d)1 1.(d)

CME Objectives

The objectives of *Neurology Alert* are:

• To present the current scientific data regarding diagnosis and treatment of neurological disease, including stroke, Alzheimer's disease, transient ischemic attack, and coma;

• To discuss the pathogenesis and treatment of pain;

• To present basic science lessons in brain function;

• To discuss information regarding new drugs for commonly diagnosed diseases and new uses for traditional drugs;

• To discuss nonclinical issues of importance to neurologists, such as the right to die and the physician's legal obligation to patients with terminal illness.

In Future Issues:

Prognosis after acute optic neuritis

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.

Stopping Statins in At-Risk Patients — Just Too Risky

In this issue: *Make sure your patients don't stop statins after a stroke or surgery; MRSA is becoming more resistant to mupirocin; new asthma treatment guidelines; and FDA approvals and warnings.*

Stopping statins, even briefly, after stroke or cardiovascular surgery increases vascular complications according to 3 new studies. Spanish investigators looked at 89 patients who were on chronic statin therapy and were admitted with acute stroke. Half were randomized to statin withdrawal for the first 3 days after admission, while the other half immediately received atorvastatin 20 mg/day. After 4 days, the statin withdrawal group was also started on atorvastatin. The primary outcome was death or dependence after 3 months as defined by modified Rankin scale of 2 or more. After 3 months, 60% of those in the statin withdraw group were disabled to the point of dependence compared with 39% of those that continued statin therapy (P = 0.043). Early neurologic deterioration was also far greater in the statin withdrawal group (65.2% versus 20.9%; $P < 0.0001$). Statin withdrawal patients also had greater infarct volume (P = 0.002). The authors conclude that statin withdrawal in the first few days after stroke is associated with a markedly increased risk of death or dependency at 90 days; hence, treatment should continue the acute phase of an ischemic stroke (*Neurology* 2007; 69:904-910).

In another study, researchers in Italy looked at stroke patients who discontinued statins after discharge from the hospital. The study population included 631 stroke patients (322 men, 309 women) without evidence of heart disease. All patients were discharged on a statin, but 38.9% discontinued the drug within 12 months. In the 12 months of follow-up, 116 patients died. After adjustment for all confounders and interactions, the hazard ratio for mortality in patients who quit a statin was 2.78 (95%CI, 1.96-3.72; P = 0.003) or nearly 3 times higher risk of death (*Stroke* 2007, published online ahead of print 8/30/07).

Another study from the Netherlands looked at a brief interruption in statin therapy associated with major vascular surgery. Nearly 300 patients on statins underwent major vascular surgery, and statin therapy was interrupted in the perioperative period in 70 patients for mean duration of 3 days. An association was observed between statin discontinuation and an increase risk of postoperative troponin release (HR 4.6) and the combination of MI and cardiovascular death combined (HR 7.5). Because many surgical patients are NPO and unable to take oral statins, and there's no intravenous statin available, the only extended release statin was tried on a subset of patients preoperatively. Patients receiving extended-release fluvastatin had fewer perioperative cardiac events compared to other statins (*Am J Cardiol* 2007; 100:316-320). The message of these studies is that statin interruption, even for a brief period during hospitalization, may lead to serious adverse events in patients at risk.

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Mupirocin Less Effective Against MRSA

Mupirocin (Bactroban) is becoming less and less effective against MRSA, even in hospitals with low levels of mupirocin use. Researchers from Washington University in St. Louis performed nasal swab cultures for MRSA in all patients admitted to their surgical intensive care unit (SICU) on admission, weekly during hospitalization, and at discharge. Of the 302 positive MRSA isolates, 13.2% were resistant to mupirocin, with 8.6% having high-level resistance. Patients with mupirocin-resistant MRSA were more likely to be older, have a history of a previous admission in last year, and had higher in-hospital mortality. The authors conclude that patients carrying mupirocin-resistant MRSA acquired it through contact with the health-care system; the strains were probably not acquired in the SICU (*Clin Infect Dis* 2007; 45:541-547). Mupirocin is commonly used to decolonize patients who are *staph aureus* carriers or have nasal colonization with MRSA. With resistance patterns increasing nationwide, this strategy may need to change.

New Guideline for Asthma Diagnosis/Management

The National Asthma Education and Prevention Program has issued an update to their clinical practice guidelines for diagnosis and management of asthma (Expert Panel Report 3 [EPR-3]). The new guideline emphasizes the importance of asthma control and highlights 4 areas of emphasis including assessment and monitoring, patient education, control of environmental factors and other asthma triggers, and pharmacotherapy. The new guideline recommends continued use of a stepwise approach to asthma control in which medication doses or types are stepped up or down as needed based on asthma control. Recommendations now are based on 3 age groups, 0-4 years, 5-11 years (a new category), and 12 years and older.. The new age group was added because of evidence that children respond differently to medications than adults. The entire guideline can be found at: http://www.nhlbi.nih.gov/guidelines/asthma/asthgdln.pdf .

FDA Actions

The FDA announced on August 14 that manufacturers of rosiglitazone (Avandia) pioglitazone (Actos), and other combination medications containing the 2 drugs will be required to add a "black box" warning to their labeling to reflect the risk of heart failure associated with the 2 drugs. Both drugs have been associated with reports of significant weight gain and edema, and some cases continuation of therapy has lead to poor outcomes including death. The black box warning advises health-care professionals to carefully observe patients taking these drugs for signs and symptoms of heart failure including rapid weight gain, shortness of breath, edema. The warning also recommends not starting either drug in patients with a history of congestive heart failure. The agency continues to review rosiglitazone for the possible increase risk of myocardial infarction associated with use of the drug.

The FDA has approved a new indication for zoledronic acid (Reclast) as a once-a-year treatment for postmenopausal osteoporosis. Reclast is administered as an annual 15-minute intravenous infusion. The drug is a bisphosphonate similar to oral bisphosphonates such as alendronate and risedronate.

Anesiva has received approval to market lidocaine topical powder intradermal injection system (Zingo) to provide local analgesic prior to venipuncture or peripheral intravenous cannulation in children ages 3-18. Zingo is a single-use helium powered system that is administered 1-3 minutes prior to needle insertion. The system is also being studied in trials of adults.

The FDA has approved a new combination of carbidopa, levodopa, entacapone (50 mg/200 mg/200 mg) for the treatment of Parkinson's disease. The new preparation helps reduce the pill burden for Parkinson's patients on multiple medications. Carbidopa/levodopa/entacapone will be marketed by Orion Corporation as Stalevo.

Omrix Biopharmaceuticals has received approval to market human thrombin (Evithrom) to promote blood clotting and control bleeding during surgery. Evithrom is the first human thrombin approved since 1954 and the only product currently available for this indication. It is applied to the surface of bleeding tissue during surgery and may be used in conjunction with absorbable gelatin sponge. Other thrombins currently on the market are derived from cattle plasma.

Nursing mothers who were taking codeine may put their babies at risk of morphine overdose if they are "ultra-rapid metabolizers of codeine," a condition that may affect up to 28% of the population. Codeine is generally recommended for nursing mothers as a cough suppressant and pain medication; however, ultra-rapid metabolizers quickly convert codeine to morphine and excrete it in breast milk. At least one infant death has been associated with this condition. The FDA has issued warning regarding codeine use by nursing mothers, recommending that mothers observe their infants closely while taking the medication for signs of morphine overdose including sleepiness, difficulty breast feeding, breathing difficulties or limpness. ■