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INSIDE

A New Genetic Cause of Amyotrophic Lateral Sclerosis

ABSTRACT & COMMENTARY

Source: Lambrechts D, et al. VEGF is a modifier of amyotrophic lateral sclerosis in mice and humans and protects motor neurons against ischemic death. *Nat Genet*. 2003;34(4):383-394.

THE CAUSE OF AMYOTROPHIC LATERAL SCLEROSIS (ALS) IS STILL an enigma. Nevertheless, genetic investigations have made considerable progress in identifying mutations associated with familial ALS (FALS). The identification of genetic alterations in patients with sporadic ALS, however, has lagged behind. The present study is a major advance in investigating the etiology of ALS. Besides a family history of ALS, age and male gender are the only established risk factors. Sporadic ALS is believed to be a multifactorial disease in which modifying genes may interact with environmental agents to affect their clinical manifestation. Lambrechts and associates previously used a genetic strategy to delete the hypoxy response element in the promotor region of the gene encoding vascular endothelial growth factor (VEGF) in mice. They demonstrated that impaired expression of VEGF predisposed mice to adult-onset progressive motor neuron degeneration with many of the neuropathological and clinical signs that occur in human ALS. It was unclear, however, whether this had any relevance to the human disease. Lambrechts et al have now extended their studies. They carried out a metaanalysis of more than 900 individuals from Sweden and 1000 individuals from Belgium and England. They now report that subjects homozygous with respect to 2 haplotypes in the VEGF promotor sequence had a 1.8 greater times risk of ALS. This was highly significant. The at-risk haplotypes had lower circulating VEGF levels in vivo and reduced VEGF gene transcription. Moreover, they carried out further studies, crossbreeding the mice with the G93A mutation and superoxide dismutase, which causes FALS with the mice deficient in VEGF. These mice died earlier due to severe motor neuron degeneration. They also demonstrated that the VEGF null mice were unusually susceptible to persistent paralysis after spinal cord ischemia and that treatment with VEGF protected the mice against ischemic motor neuron death.

VOLUME 22 • NUMBER 2 • OCTOBER 2003 • PAGES 9-16

COMMENTARY

These studies are very important in identifying a risk factor, which may be important in patients with sporadic ALS. They are the first to find a genetic risk factor and have clearly demonstrated that having 2 different polymorphisms in the promotor of the VEGF gene increases the risk of ALS 1.8-fold. Calculation of the population attributable risk indicated that the influence of the VEGF at-risk genotypes resulted in net increases in the total number of individuals by 5.7%, 5.6%, and 10.4% in the Swedish, Belgian, and Birmingham populations, respectively. This is greater than the role of mutations in SOD1, which are responsible for approximately 2% of the entire ALS population. This study of almost 2000 individuals is the largest genetic association study with ALS that has thus far been performed. These studies in mice, which show that the VEGF-deficient mice are more sensitive to minor ischemic insults and that VEGF protects against ischemic motor neuron death, support a functional role of VEGF. Prior studies have shown a role of VEGF in neuronal survival, regeneration, growth, and axonal outgrowth. The findings raised the intriguing question as to whether long-term treatment with VEGF might have some efficacy in treating adult-onset motor neuron disease. — **M. FLINT BEAL**

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Predictive Accuracy of MRI Prognosticators in the Early Detection of Malignant MCA Infarcts

ABSTRACTS & COMMENTARY

Sources: Thomalla GJ, et al. Prediction of malignant middle cerebral artery infarction by early perfusion- and diffusion-weighted magnetic resonance imaging. *Stroke*. 2003;34:1892-1899; Wijman CA [editorial]. Can we predict massive space-occupying edema in large hemispheric infarctions? *Stroke*. 2003;34:1899-1900.

PATIENTS WITH MASSIVE INFARCTS IN THE MIDDLE cerebral artery (MCA) territory may develop brain edema leading to midline shift, raised intracranial pressure, and downward herniation. Their clinical course is characterized first by a deterioration in the level of consciousness and then an orderly rostrocaudal brainstem failure as herniation progresses, usually 2-5 days after the ictus. This subgroup of MCA infarcts has been labeled malignant MCA infarction (MMI).[1] At present, there is no universally accepted treatment modality for patients who deteriorate as a result of MMI. Hemicraniectomy with dural patch enlargement has been proposed as life saving, and the measure is being studied as a therapeutic option. In 2 nonrandomized controlled studies from the same group of investigators,[2,3] mortality was reduced and functional outcome in the survivors in the hemicraniectomy group was improved compared with historic controls. Nevertheless, at present, without a randomized control study, it remains uncertain as to whether the quality of life in survivors is acceptable enough to advocate surgical treatment for patients with acute strokes, particularly those who are elderly and those with dominant hemisphere infarctions. Nevertheless, if hemicraniectomy proves to be useful in patients with life-threatening edema from stroke, it is obvious that early surgery will result in the best clinical outcomes. Therefore, early and accurate prediction of MMI will be crucial in the management of such patients.

In the present article, Thomalla and colleagues report on the predictive value of early perfusion-weighted magnetic resonance imaging (PWI) and diffusion-weighted magnetic resonance imaging (DWI) within 6 hours of stroke onset in 37 patients with MCA stroke and a proximal vessel occlusion, either the carotid-T or MCA stem. Patients developed MMI defined by a decline in consciousness demonstrated as a loss of at least 1 point on

the level of consciousness item on the NIH Stroke Scale and radiologic signs of space-occupying brain edema following a large infarct with compression of the ventricles or a midline shift. Thomalla et al found that an apparent diffusion coefficient < 80% (ADC < 80%) > 82 mL was the most accurate MRI prognosticator predicting MMI with 87% sensitivity and 91% specificity. Admission NIH Stroke Scale score had a higher sensitivity than any single MRI prognosticator but had only moderate (72%) specificity. Three patients, however, were misclassified as MMI with the use of the 82 mL (ADC < 80%) cut off. Thomalla et al conclude that MRI can help in the selection of patients for early craniectomy or other aggressive therapeutic approaches before the onset of clinical deterioration.

COMMENTARY

Previous studies have used clinical signs to predict the development of MMI. Coma on admission and early nausea and vomiting have been found to correlate with fatal brain edema. The initial NIH Stroke Scale score at admission was higher in patients who died or were dependent at 1 month after stroke. In the present study, Thomalla et al found that an NIH Stroke Scale score > 19 was highly sensitive to the prediction of MMI; however, the specificity of this clinical score was low. In other studies, the site of vessel occlusion has been reported to predict fatal brain swelling with high specificity of greater than 80% but with low sensitivity of about 50%. Therefore, neither clinical assessment nor site of vessel occlusion allows for the reliable prediction of MMI.

Thomalla et al focused on the 6-hour time window because at this early stage of stroke development, therapeutic decisions must be made concerning hemicraniectomy. They found that MRI-derived parameters resulted in good prediction of MMI, but, nevertheless, 3 patients who had large infarctions with edema and midline shift who remained clinically stable were misclassified as MMI. Therefore, if this study had been a therapeutic trial of hemicraniectomies, these patients would have been subjected to an unnecessary surgical treatment.

In addition, as Thomalla et al admit, there were limitations to their study. It used a retrospective design, was not a community-based study, and enrolled only a small sample of patients. Therefore, validation of these results will depend on a multinational prospective study of MRI prognosticators in MMI patients. — **JOHN J. CARONNA**

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Stroke Risk of Inherited Thrombophilia is Low

ABSTRACTS & COMMENTARY

Sources: Jerrard-Dunne P, et al. Ethnic differences in markers of thrombophilia. *Stroke*. 2003;34:1821-1826; Hankey GJ, Eikelboom JW [editorial]. Routine thrombophilia testing in stroke patients is unjustified. *Stroke*. 2003;34:1826-1827.

THE TERM "THROMBOPHILIA" IS COMMONLY USED TO describe disorders of the hemostatic mechanisms that are likely to predispose to thrombosis. Examples of inherited factors are deficiency of protein C, protein S, or antithrombin; activated protein C resistance resulting from the Factor V Leiden mutation; and the prothrombin gene (20210G/A) mutation and dysfibrinogenemia. The acquired thrombophilias include the lupus anticoagulant and the anticardiolipin antibodies. Of mixed or unknown origin are high levels of coagulation factors VIII, IX, or XII, among others. The prevalence of inherited thrombophilic states shows a marked interethnic variation. For example, at least one thrombophilic disorder is present in 10-15% of the white population of Western Europe. Data on the normal reference ranges for inherited thrombophilias in the black community are lacking, however. Individuals of African and African-Caribbean descent have a higher incidence of ischemic stroke compared with whites and present with stroke at a younger age. Therefore, Jerrard-Dunne and associates estimated the ethnic-specific reference ranges in a community population to determine the prevalence of thrombophilic states in a multiethnic stroke population. They determined the levels of inherited and acquired markers of thrombophilia in 130 consecutive ischemic stroke patients 65 years of age or younger. The populations included 15 black Caribbeans, 30 black Africans, 50 whites, and 130 community controls. Black African controls had significantly lower protein S and protein C levels and a trend to lower antithrombin III levels compared with white controls. Black Caribbean and African controls had his/her diluted Russell's viper venom time ratios compared with whites. In ethnic-specific reference ranges, 8 controls and 11 stroke patients had thrombophilic abnormalities. The study demonstrated significant ethnic differences in normal ranges for markers of thrombophilia. Using the normal reference ranges determined from a white population, a significant proportion of healthy black community controls would be classified as having abnormal thrombophilia screening. When appropriate reference ranges were used, thrombophilia was not a significant

risk factor for stroke either overall or in any of the 3 ethnic groups studied.

COMMENTARY

As pointed out in Hankey and Eikelboom's accompanying editorial, thrombophilias are an established independent causal risk factor for venous thromboembolism (VTE) and may account for a substantial proportion of cases of recurrent VTE. For example, in contrast to community controls, a thrombophilic disorder is present in as many as 30% of unselected individuals with VTE and 50-70% of those with recurrent VTE.[1] Clinical management of patients with thrombophilia and VTE differs slightly from that of individuals with VTE without thrombophilia. Both groups usually are treated with anticoagulation for a period of time, but patients who have a thrombophilia that predisposes to further episodes of VTE may be treated with anticoagulation indefinitely. In contrast to these cases of VTE, the prevalence of inherited thrombophilia in patients with ischemic stroke is not different from that among the general community. Therefore, the role, if any, of inherited thrombophilia in the causation of ischemic stroke is uncertain. In the present paper, Jerrard-Dunne et al found that 6% of community controls and 8.5% of ischemic stroke cases had a thrombophilia. Similar results have been obtained by others and indicate that inherited thrombophilias account for < 10% of cases of ischemic stroke. An exception to this statement is that prevalence of the acquired thrombophilias, the lupus anticoagulant, and anticardiolipin antibodies is significantly higher in arterial thromboses compared with controls and appears to be an independent predictor of stroke.[2] The data suggest that the risk conferred by an inherited thrombophilia for ischemic stroke is likely to be low overall and almost nonexistent in some ethnic groups such as individuals of African or African-Caribbean descent. The risk may be higher in some particular subtypes of stroke, like thromboembolism from venous stasis via a right-to-left shunt such as a patent foramen ovale or pulmonary AV fistula. Nevertheless, in such patients with stroke caused by thromboembolism from venous or cardiac source, long-term anticoagulation is likely to be instituted regardless of the presence or absence of a thrombophilia. Certainly, there appears to be no justification for the routine screening for thrombophilia in most patients, especially older patients with ischemic stroke, in the absence of any reliable data linking the inherited thrombophilias to a particular subtype of ischemic stroke or to a favorable response to a particular intervention. — **JOHN J. CARONNA**

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Unraveling Cryptogenic Stroke

ABSTRACT & COMMENTARY

Source: Bang OY, et al. Frequency and mechanisms of stroke recurrence after cryptogenic stroke. *Ann Neurol*. 2003;54:227-234.

STROKE WITH NO DETERMINED CAUSE, OR CRYPTOGENIC stroke [CS], accounts for nearly 40% of all ischemic strokes, a staggering percentage given the resources and technologies used as part of stroke evaluation. Traditionally, it has been held that CS carries a more benign prognosis than other stroke subtypes such as large artery disease [LAD] or cardioembolic disease [CE]. However, until this recent study, the long-term risk of recurrent stroke in this large segment of the stroke population had never been prospectively studied.

Bang and associates identified 204 patients after an index stroke and classified them among 5 stroke subtypes: small artery disease [SAD], LAD, CE, 2 or more causes, and no determined cause [NC]. Stroke recurrence was reported over the following 1-year period. Stroke recurrence rates were significantly higher in the NC group, 30% compared to 16% in the LAD group, 14% in the CE group, and 2% in the SAD group. Furthermore, in 6 of 11 NC recurrent stroke patients, an association with intracranial atherosclerosis [IA] was found. There was found to be moderate stenosis [30-50%] of a symptomatic vessel or significant [greater than 50%] stenosis of a nonrelevant artery. All the recurrent strokes in the NC group occurred in the territory of a stenosed intracranial artery or at the same site as the index stroke, lending some credence to their suggestion that IA might be the mechanism of stroke in these patients. They also noted that the NC group had recurrences throughout the year of the study, while the other subtypes showed recurrence often within the first month. Bang et al conclude that a subset of CS actually represents a mild form of large artery atherosclerosis. The implication is that early detection of such vascular lesions might be crucial in preventing recurrent stroke in these patients.

COMMENTARY

The study is limited by a small number of patients and a lack of a transesophageal echocardiogram evaluation in some patients. Anomalies as a PFO, atrial thrombus, or vegetations are not adequately excluded. This report is important, however, as it emphasizes that CS is not a homogenous disease with a benign prognosis. Rather, CS accounts for a significant proportion of ischemic stroke and has a higher 1-year recurrence rate than previously reported. Secondary stroke prevention in this group is, therefore, crucial and requires that we better understand the pathophysiology of this disease. Bang et al make a step toward that goal, finding that intracranial atherosclerosis may be a mechanism of stroke in some patients with CS. Treatment implications of this certainly include aggressive risk-factor reduction (such as statin therapy), and anticoagluation with warfarin is possibly warranted. — **SHYAM PRABHAKARAN AND ALAN Z. SEGAL**

Dr. Prabhakaran is Chief Resident in Neurology at Cornell University Medical College, New York, NY.

When Can People With Epilepsy Drive?

ABSTRACT & COMMENTARY

Source: Drazkowski JF, et al. Seizure-related motor vehicle crashes in Arizona before and after reducing the driving restriction from 12 to 3 months. *Mayo Clin Proc*. 2003;78: 819-825.

When is it safe to sit behind the wheel if you've just had a seizure? Specific seizure-free intervals vary from state to state. In this time-trend study, an analysis was undertaken to determine if lowering the interval from 12 months to 3, as was done in Arizona, negatively impacted on motor vehicle accident (MVA) frequency. Seizure-related MVAs were defined as such if the patient self-reported a seizure at the time of the accident, was witnessed to have a seizure or was confused at the scene in the absence of head trauma, or had low antiepileptic drug levels as reported by hospital personnel. Non seizure-related MVAs included cardiac-related crashes due to arrhythmia or myocardial infarction and diabetes-related MVAs as documented by hypoglycemia, altered consciousness, or response to intravenous glucose at the scene. Psychiatric conditions, medication effects, stroke, visual impairment, dementia, and migraine comprised other medically related MVAs. Crash incidence rates were obtained by dividing the number of MVAs by the number of miles driven, as estimated from the Arizona State Motor Vehicle Department annual report.

Approximately 614,000 MVAs were reported during the 6-year study period, 859 of which were medically related. Comparing 1991-1993, when a 12-month seizure-free interval was required, to 1994-1996, when the interval was lowered to 3 months, the number of seizure-related MVAs increased slightly from 125 to 136. Based on incidence rate, however, seizure-related MVAs dropped by 2%, not a significant difference, despite an 8% increase in MVAs overall. Fatality incidence dropped by 64%, but injuries associated with seizure-related MVAs increased 31%. No significant change was evident in mean age of driver (37 vs 38 years of age), percentage of urban accidents, or percentage of single- vs multiple-car MVAs. Arizona's excellent weather patterns and road conditions precluded inclement weather or road surface from playing a role in any crash. MVAs related to other medical conditions similarly showed no significant change. Common sense must always prevail, but limiting driving restriction to 3 months following a seizure appears safe and reasonable.

COMMENTARY

This report supports the consensus developed at a symposium held in Quebec City in November 1998, regarding epilepsy and driving.[1] Attendees included an invited international group of neurologists from Canada, the United States, and Europe; Canadian licensing representatives; and delegates from the Canadian Council of Motor Transport, the Canadian Medical Protective Association, and the Canadian Medical Association. Among the medical experts, abolition of mandatory reporting of epilepsy to the Motor Vehicle Department (as is the law in Canada) was felt to be desirable. Most patients, it was felt, could return to driving private automobiles within 6-12 months of seizure freedom. First and foremost, observance of local laws remains paramount until changes are appropriately legislated. — **MICHAEL RUBIN**

Reference

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IVIG Pre-Thymectomy

ABSTRACT & COMMENTARY

Source: Huang CS, et al. Intravenous immunoglobulin in the preparation of thymectomy for myasthenia gravis. *Acta Neurol Scand*. 2003;108:136-138.

Six consecutive myasthenia gravis patients, one man and 5 women, aged 21-68, underwent intra-

venous immunoglobulin (IVIG) infusion in preparation for thymectomy. The purpose was to determine, in this unblinded trial, whether IVIG was beneficial to outcome. No one was in myasthenic crisis nor had any functional pulmonary impairment. Mean disease duration was approximately 7 months (range, 2-17 months), and diagnosis was based on clinical, electromyographic, and acetylcholine receptor antibody criteria. Pyridostigmine had been the only preoperative medication prior to the IVIG, which was infused over 5 days at a dose of 0.4 mg/kg/d. Transternal thymectomy was performed in all.

All patients benefited from IVIG within a mean of 3.33 days (range, 1-9 days). Pyridostigmine requirements decreased, thymectomy was performed within a mean of 11 days (range, 9-13), and the postoperative courses were uneventful with extubation successfully undertaken by 8 hours (mean, 6.7 hours). Reintubation was never required. Improvement was sustained postoperatively for 2 weeks in all patients and for 6 and 10 weeks in 4 and 3 cases, respectively. One patient who initially improved preoperatively with IVIG deteriorated and required plasma exchange prethymectomy. None of the remainder required plasma exchange, steroids, or immunosuppressants pre- or postoperatively. IVIG appears safe and effective in the preoperative preparation for thymectomy. Larger controlled trials comparing IVIG to plasma exchange would be the logical next step in confirming and extending these results.

COMMENTARY

Thymectomy, though widely recommended for the treatment of autoimmune myasthenia gravis, remains a treatment without controlled prospective studies to support its role. Such a trial, comparing immunosuppression with and without thymectomy, has been recommended by the American Academy of Neurology and is being developed.

Thymectomy may be performed by various techniques. Transcervical thymectomy, even without removal of all the cervical and mediastinal perithymic fat, is felt by some, based on retrospective study, to be comparable to transternal thymectomy.[1] Others report, again based on retrospective data, that partial sternotomy with removal of the entire thymus and the surrounding fat yields results "similar to the literature data."[2] Close examination of the data, however, does not support these conclusions.[3] Life-table analysis indicates that combined transternal and transcervical thymectomy produces greater remission rates than any of the above methods (ibid). Prospective study comparing the different techniques is desirable and warranted. Although randomized study would make recruitment difficult, a prospective, nonrandomized study is a doable and attractive alternative. — **MICHAEL RUBIN**

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Eletriptan vs Sumatriptan: Let's Get Ready to Rumble?

ABSTRACT & COMMENTARY

Source: Farkklia M, et al. Eletriptan for the treatment of migraine in patients with previous poor response to oral sumatriptan. *Cephalalgia*. 2003;23:463-471.

The triptan wars are heating up with 7 competitors now on the market all backed by the heaviest of the pharma heavyweights. Unfortunately, the overall migraine market has not expanded—meaning far too few migraine patients are being diagnosed and adequately treated. Hence, the pharmaceutical industry has been left trying to capture the triptan market share from one another. Despite, or perhaps in spite of, the soaring pharmaceutical marketing budgets, clinicians remain wondering, "Which is the best triptan?" And the answer is, "None of them." That is to say, they all work and they all work well. It just depends upon the patient. As with other large therapeutic categories, efficacies among similar drugs are most dependent upon variability between individuals.

As such, we report on the findings of Farkkila and colleagues looking at eletriptan response rates in a cohort of migraine patients previously unresponsive or intolerant to sumatriptan. In a double-blind, placebo-controlled, parallel-group, multicenter study using usual headache study end points, 446 total patients were evenly divided into 40 mg, 80 mg, and placebo groups and followed for up to 3 migraine attacks. As stated, all these patients had proven intolerant by side effects or unresponsive to sumatriptan. Two-hour pain relief response was 59% for 40 mg and 70% for 80 mg compared to 30% for placebo ($P < .0001$). Consistency of response was observed in at least 2 of 3 attacks in 66% (40 mg) and 72% (80 mg) vs 15% for placebo ($P < .001$). Discontinuation rates for side effects were infrequent to none but nausea, asthenia, and chest pain were reported < 10%.

COMMENTARY

So does this prove eletriptan is better than sumatriptan? No, of course not. Both are good triptans and both work well in the patients for whom they work. One may quibble about exactly how "sumatriptan intolerance or unresponsiveness" was defined. But that would lose sight of the forest. The bigger theme here is that patients do well with triptans, and if they fail one they should be given trials of the others until they respond. We at the Cornell Headache Service welcome both eletriptan into the headache armamentarium for patients unresponsive to sumatriptan, as well as sumatriptan for patients unresponsive to eletriptan. — **JEFFREY REICH**

Will Sage Oil Make You Wiser?

ABSTRACTS & COMMENTARY

Sources: Perry NS, et al. *Salvia* for dementia therapy: Review of pharmacological activity and pilot tolerability clinical trial. *Pharmacol Biochem Behav*. 2003;75:651-659; Tildesley NT, et al. *Salvia lavandulaefolia* (Spanish Sage) enhances memory in healthy young volunteers. *Pharmacol Biochem Behav*. 2003;75:669-674.

In 1597, the herbalist John Gerard reported that an extract of the sage plant, "is singularly good for the head and brain and quickeneth the nerves and memory." More than 400 year later, British investigators have put Gerard's observation to the test by examining the effects of an essential oil derived from Spanish sage (*Salvia lavandulaefolia*) on memory in normal volunteers and patients with Alzheimer's disease (AD). Researchers from the Medicinal Plant Research Centre (MPRC) at the Universities of Newcastle and Northumbria hypothesized that sage oil extract would improve memory acutely in normals and have positive long-term effects on AD patients. Their rationale included past reports in the herbal literature about sage's cognitive-enhancing effects and recent studies of sage oil's antioxidant, anti-inflammatory, and acetylcholinesterase inhibitory properties.

Tildesley and associates carried out 2 crossover studies of sage oil in normals—one with a pseudo-randomized design in 20 volunteers and another doubleblind, placebo-controlled investigation in 24 additional subjects. A computerized cognitive test battery was administered 4 times over a 6-hour period to assess immediate and delayed verbal recall abilities before and after sage oil ingestion. One hour after oral administration, a dose of 50 µL of sage oil was reportedly associated with a statistically significant change from baseline in immediate verbal recall performance relative to placebo. Effects at other times and doses were not consistently observed across trials. No adverse effects were observed in normals with single doses up to 150 µL.

Perry and colleagues reported results of an open-label trial in 11 patients with mild-to-moderate AD who initially received 50 µL per day of sage oil and were titrated over 3 weeks to 50 µL t.i.d. Outcome was assessed at 6 weeks using the Folstein Minimental State (MMSE) examination, a computerized cognitive test battery and the Neuropsychiatric Inventory. No significant changes were observed in immediate recall, delayed recall, or the MMSE. The NPI and tests of attention and vigilance were reported to improve after 6 weeks of treatment with sage oil. Two patients with a past history of hypertension experienced significant increases in blood pressure during the trial. The study also examined the degree of peripheral red blood cell acetylcholinesterase (AChE) inhibition brought about by sage oil treatment and found a 14% inhibition of AChE at 150 µL/d. Perry et al found the results encouraging and expressed the belief that further studies are warranted to establish the value of sage oil as a treatment for AD.

COMMENTARY

While it is encouraging to see herbal medicines being investigated with rigorous clinical scientific methodology, these studies fall short of supporting their conclusions concerning the value of sage oil in improving human cognition. In the trials involving normal adults, baseline memory performance was substantially lower in the sage oil-treated arms than with placebo. This difference in memory performance at baseline was actually greater than the magnitude of the reported change in memory performance after treatment. Although such baseline differences can be adjusted for analytically, the reported changes in memory performance with 50 µL doses of sage oil could well represent regression to the mean rather than a true biological effect.

The open-label trial is clearly inadequate to establish whether sage oil is beneficial in the treatment of AD patients. The duration was too short, especially since AD clinical trials frequently show a placebo effect at 6 weeks. This is particularly problematic in an open-label study with an exceedingly small number of subjects and an accordingly greater potential for biased outcome. The 14% inhibition of AChE observed in this study indicates relatively weak cholinesterase inhibition relative to approved AD treatments. Despite Perry et al's con-

tention that sage oil is a more benign intervention than currently available AD therapies, the occurrence of treatment-related hypertension in 2 of 11 AD patients receiving sage oil at doses of 150 µL per day suggests that this herbal preparation is not without potential side effects.

Unquestionably, sage can add to the taste of turkey stuffing, stews, and salads. The medicinal value of sage oil, however, remains to be determined. — **NORMAN RELKIN**

Audio Conference

Seasonale: A Revolutionary Contraceptive

EXTENDED HORMONAL CONTRACEPTION IS DRAWING dramatic attention due to the desire of many women to reduce or eliminate the number of withdrawal bleeds associated with current birth control methods. The first extended-use oral contraceptive, Seasonale, was just approved by the FDA and is expected to have an enormous effect on family planners and OB/GYNs. This new therapy will reduce the number of periods a woman has to 4 a year. Researchers also are looking at extended use of the NuvaRing contraceptive vaginal ring and the Evra transdermal contraceptive patch.

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"I consider [Seasonale] to be the most important change in hormonal contraception since birth control pills initially became available," says Robert Hatcher, MD, MPH, editor of *Contraceptive Technology Update*, and professor of gynecology and obstetrics at Emory University.

Presenters will be Hatcher, who will act as moderator; Lee Shulman, MD, professor of OB/GYN at Northwestern University, Chicago; and Sharon Schnare, RN, FNP, CNM, MSN, a family planning clinician and consultant in Seattle.

After listening to this program, participants will be able to:

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- identify best candidates for extended-use hormonal contraception.

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CME Questions

13. All of the following features correlate with the development of MMI in acute stroke patients *except*:
a. high NIH Stroke Scale score.
b. occlusion of the MCA mainstem.
c. early nausea and vomiting.
d. coma on admission.
e. older age and male sex.

14. All of the following are inherited thrombophilias *except*:
a. protein C deficiency.
b. protein S deficiency.
c. Factor V Leiden.
d. anticardiolipin antibodies.
e. the prothrombin gene G/A mutation.

15. Patients with epilepsy:
a. should never drive again.
b. may usually safely return to driving after a 3-month seizure-free interval, if the law so allows.
c. require an 18-month seizure-free interval before driving might be permitted.
d. may drive as soon as their antiepileptic drug blood levels are therapeutic.
e. should have 3 normal EEGs before resuming driving.

Answers: 13(e); 14(d); 15(b)

In Future Issues:

Glia Cells Enter Stage Right