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Benign Partial Seizures of Adolescence—A Common Disorder Rarely Described

ABSTRACT & COMMENTARY

Source: King MA, et al. Benign partial seizures of adolescence. *Epilepsia* 1999;40(9):1244-1247.

Periodically, neurologists stumble across a disease that may be fairly common, yet is not well known. Such is the case for the diagnosis of benign partial seizures of adolescence (BPSA). Originally described by Loiseau and Orgogozo in 1978 (Loiseau P, Orgogozo JM. *Lancet* 1978;2:1070-1071), the syndrome received relatively little attention until now. Loiseau and Orgogozo originally described a retrospective series of 145 patients who first experienced a seizure or cluster of seizures of focal onset that did not recur for at least five years. Seizures frequently secondarily generalized. The EEG of these patients was typically normal or had non-focal abnormalities. These patients with BPSA constituted 24% of a group of retrospectively selected patients who experienced a first focal seizure between 12 and 18 years of age. Although the syndrome found its way into textbooks, few data have been collected on this group of patients prior to the current prospective study of King and colleagues.

From a database of 300 consecutive patients older than 5 years of age who presented with a first unprovoked seizure, King et al identified 92 who were between 10 and 20 years old. Of this group, 37 (40%) had partial epilepsy, 45 (49%) had generalized epilepsy, and 10 could not be classified. Of the patients with partial epilepsy, eight (22%) satisfied the diagnostic criteria of Loiseau and Orgogozo for BPSA. By way of comparison, four patients (11%) were diagnosed with benign Rolandic epilepsy, a well-known syndrome of childhood, five patients had structural lesions accounting for their seizures (14%). Ten patients (27%) had temporal lobe epilepsy, a common seizure type that may begin in adolescence.

The features of BPSA were the following: 1) seizures beginning focally followed by a sensory or motor 'march' and frequent generalization; 2) normal MRI; 3) absence of a family history of seizure; 4) neurologically normal with no history of antecedent illnesses that might predispose to seizures; 5) normal interictal EEGs, except for

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two EEGs recorded within eight hours of a seizure, that expressed focal paroxysmal discharges. Patients were followed between 2-3.2 years. Three patients received treatment with carbamazepine. In follow-up, four patients had no further seizures and three others had persistent occasional simple seizures. One patient developed recurrent tonic-clonic seizures after carbamazepine was slowly tapered. King et al conclude that adolescent patients who present following a first unprovoked seizure characterized by a sensory or motor march, and who have a normal brain MRI, are likely to have a good outcome to their illness.

COMMENTARY

This study offers a method of distinguishing patients with new-onset focal seizures and a good prognosis from patients presenting in a similar manner in whom the prognosis is more guarded. As King et al note, the presence of focal sensory or motor seizures with description of a march of symptoms raises the clinician's concern for an organic lesion. In this report, King et al update the description of BPSA first presented by Loiseau and Orgogozo and offer prospective evidence that this entity is more common than epileptogenic structural lesions. Armed with these results, clinicians will be better prepared to decide whether to treat and to offer reassurance to patients and families. **—fal & slm** (*Dr. Solomon L. Moshé is Professor and Director, Pediatric Neurology and Clinical Neurophysiology, Department of Neurology, Montefiore Medical Center-Albert Einstein College of Medicine.*)

Neurology Alert, ISSN 0741-4234, is published monthly by American Health Consultants, 3525 Piedmont Rd., NE, Bldg. 6, Suite 400, Atlanta, GA 30305.

VICE PRESIDENT/ GROUP PUBLISHER: Donald R. Johnston.
EXECUTIVE EDITOR: Glen Harris.
MARKETING PRODUCT MANAGER: Schandale Kornegay.
ASSISTANT MANAGING EDITOR: Robin Mason.
COPY EDITOR: Neill Larmore.

GST Registration Number: R128870672.
Second class postage paid at Atlanta, GA.
POSTMASTER: Send address changes to ***Neurology Alert,*** P.O. Box 740059, Atlanta, GA 30374.

Back issues: $35. Missing issues will be fulfilled by Customer Service free of charge when contacted within one month of the missing issue's date.

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Editorial E-Mail Address: neill.larmore@medec.com
World-Wide Web: http://www.ahcpub.com

Subscription Prices

United States
$209 per year (Student/Resident rate: $105).
Multiple Copies
1-9 additional copies: $188. 10 or more copies: $167.
Canada
Add GST and $30 shipping.
Elsewhere
Add $30 shipping.

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Globus Pallidus Deep Brain Stimulation for Dystonia

ABSTRACT & COMMENTARY

Source: Kumar R, et al. Globus pallidus deep brain stimulation for generalized dystonia: Clinical and PET investigation. *Neurology* 1999;53:871-874.

The current treatment of dystonia includes pharmacotherapy (principally treatment with anticholinergics, baclofen, and clonazepam) and botulinum toxin injections. While they are often effective, many patients with dystonia obtain little to no relief from these approaches. Kumar and colleagues report their encouraging experience with bilateral pallidal deep brain stimulation in a patient with idiopathic generalized dystonia.

At the age of 32, their patient developed symptoms of dystonia, which gradually worsened despite treatment with conventional medical therapy and botulinum toxin injections. Genetic testing was not performed and there was no family history of dystonia or neuroleptic exposure. At the age of 49, she was completely disabled and unable to work. Her dystonia was generalized, involving the face, neck, arms, feet, and trunk.

She underwent bilateral same-sitting implantation of internal globus pallidus stimulators under microelectrode guidance. After determination of the optimum settings of the implanted pulse generators, double-blind patient examinations revealed marked immediate bilateral improvement in her dystonia. Dystonic symptoms improved by 65%, as measured by the standard clinical rating scale for dystonia, the Burke-Fahn-Marsden scale. Unilateral stimulation of the right GPi improved contralateral limb posturing and left truncal tilt. Unilateral stimulation of the left GPi improved facial dystonia and blepharospasm. The effects of bilateral stimulation were additive.

One year after electrode implantation, the patient underwent (15O)H_20 PET scanning. This technique measures changes in cerebral blood flow, and, by inference, cerebral cortical activation. Prior studies have shown that primary and association motor cortices are excessively activated by such maneuvers in patients

with dystonia. Scans taken in this patient during performance with the joystick showed suppression of abnormal activation of motor and supplemental motor areas, i.e., restoration of the normal pattern of cortical activation during movement.

The beneficial effects of stimulation were maintained for more than one year. However, hardware malfunction on one side and contralateral erosion of the scalp over the other electrode required removal of both stimulators and loss of therapeutic benefit.

COMMENTARY

Several features of this paper merit comment. Four decades ago, Irving Cooper opened the field of stereotaxic surgery for dystonia by performing cryothalamotomies on patients with generalized dystonia. While his patients often experienced dramatic intraoperative benefit, these results were often short-lived. Bilateral thalamotomies produced severe speech disturbances in more than 25% of patients, and this approach soon fell out of favor. With the resurgence of interest in pallidal surgery for Parkinson's disease, there has been growing interest in pallidal surgery for patients with intractable dystonia.

Experience with pallidotomy and pallidal stimulation for dystonia is limited, with fewer than 100 patients reported in the literature. Several critical questions remain to be answered. The most important issue is the selection of appropriate candidates for the procedure. Given the inherent risks of deep brain surgery, only patients with intractable generalized dystonia should be considered for this procedure. Patients with DYT-1 dystonia (Oppenheim's dystonia) probably do better with these procedures than patients with secondary dystonia. Results of pallidotomy in patients with secondary dystonia have been disappointing. While immediate improvement was seen with stimulation in this report, several patients with DYT-1 dystonia have enjoyed delayed improvement after bilateral single-sitting pallidotomy. These patients continued to improve for weeks to months after the procedure, suggesting more permanent changes in cortical connectivity.

Finally, the question remains whether pallidotomy or pallidal stimulation is preferable for these patients. Pallidal stimulation offers several advantages; bilateral procedures can be performed without undue risk of neurobehavioral catastrophes, and stimulation parameters can be optimized to produce the maximum clinical benefit. The drawbacks of stimulation were evidenced in this patient-hardware failure and erosion of the scalp lead, requiring removal of the devices. **—sf** (*Dr. Steven Frucht is Assistant Professor of Neurology, Movement Disorders Division, Columbia-Presbyterian Medical Center.*)

Will to Live in the Terminally Ill

ABSTRACT & COMMENTARY

Source: Chochinov HM, et al. Will to live in the terminally ill. *Lancet* 1999;354:816-819.

Chochinov and colleagues examined the extent to which will to live may fluctuate among terminally ill cancer patients as death approaches. Of 585 patients admitted to a Palliative Care Unit in Winnipeg, Manitoba, Canada, 168 met enrollment criteria of a MMSE score of 21 or higher and a sufficiently strong physical condition to participate in the study at several points in time. Chochinov et al used the Edmonton System Assessment System, a self-report instrument that consists of a series of visual analogue scales designed to measure the following symptoms among inpatients in a palliative care unit: pain, anxiety, depression, sense of well-being, dyspnea, drowsiness, nausea, activity, and appetite. A will-to-live visual analogue scale was added with "complete will to live" and "no will live to live," respectively reflected as the lowest and highest marks on the scale. Maximum and median differences in will to live were calculated for each individual over consecutive 12-hour, 24-hour, 7-day, and 30-day intervals. Several multiple regression models were constructed to evaluate the relationship between will to live and various common symptoms of distress at 12 hours, 24 hours, 1 week, 2 weeks, 3 weeks, and 4 weeks since entry into the study. The pattern of median changes in will to live over the various time intervals was stable. However, the maximum fluctuation in each individual patient's will-to-live score showed wide variation even between very short time intervals. Analysis of the multiple regression models revealed that while psychological variables (anxiety, depression) were predictors of will to live at the earlier points in time, as the patients came closer to death physical symptoms (dyspnea) replaced the psychological factors as mediators in the patient's desire to live.

COMMENTARY

The substantial fluctuations among the individuals in this study suggested to Chochinov et al that will to live among terminally ill cancer patients is highly unstable. While other studies have demonstrated an association between support for physician-assisted suicide and depression and pain, this is the first investigation of will to live over time in a significant number of terminally ill patients. (Chochinov HM, et al. *Am J Psychiatry* 1995;152:185-191; Foley KM. *J Pain Symptom Manage*

1991;6:289-297.) These findings raise important implications for the ongoing debate regarding the legalization of physician-assisted suicide and pose a challenge to the medical community to pay vigorous attention to symptom control in the care of dying patients. **—ac** (*Dr. Alan Carver is a Pain and Palliative Care Fellow in the Department of Neurology at Memorial Sloan-Kettering Cancer Center.*)

Therapeutic Benefit: Aspirin Revisited in Light of the Introduction of Clopidogrel

ABSTRACT & COMMENTARY

Source: Gorelick PB, et al. Therapeutic benefit: Aspirin revisited in light of the introduction of clopidogrel. *Stroke* 1999;30:1716-1721.

Aspirin is currently the standard of care for stroke prevention in patients with identified atherothrombotic disease. Ticlopidine (Ticlid), a potentially more efficacious drug than aspirin, has been available as alternative therapy, but serious side effects such as neutropenia limit its usefulness. Now, clopidogrel (Plavix), a thienopyridine derivative similar to ticlopidine, offers similar efficacy, with fewer side effects.

Clopidogrel was recently compared with aspirin in the Clopidogrel versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) trial. Among patients with recent MI, stroke, or significant peripheral vascular disease, CAPRIE found an event rate of 5.83 events per year in the aspirin-treated groups vs. 5.32 events per year in the clopidogrel-treated group (P = 0.043), an 8.7% relative risk reduction. CAPRIE used a combined end point of ischemic stroke, MI, or vascular death.

A secondary subgroup analysis in CAPRIE showed that not all patients benefited equally. The largest benefit of clopidogrel, accounting for 75% of its therapeutic advantage, occurred in the group with peripheral arterial disease. The relative risk reduction in these patients was 23.8% compared to 7.3% for those with stroke (95% CI-5.7-18.7; P = 0.26, a nonstatistically significant difference).

Gorelick and colleagues review the safety profiles of clopidogrel compared with aspirin. Clopidogrel does not cause significant neutropenia, although long-term data are not available for this drug. Observations are limited to three years. By contrast, aspirin has been in use for more than 100 years. The CAPRIE study used 325 mg of plain aspirin. Enteric-coated aspirin (the most commonly prescribed form) or low-dose aspirin (probably of equal efficacy) may have compared even more favorably with clopidogrel.

Clopidogrel is considerably more expensive than aspirin (45-fold cost differential) and remains 5- to 7-fold more costly when costs to prevent an event or save a life are calculated. Patient compliance may also be influenced by the higher drug cost of clopidogrel.

Analyzing efficacy, safety, and cost, Gorelick et al conclude that aspirin should remain first-line therapy in this setting. As Gorelick et al observe, however, clopidogrel is a viable alternative, particularly for patients who fail aspirin or cannot tolerate it. **—azs** (*Dr. Alan Z. Segal is Assistant Professor, Department of Neurology, Weill-Cornell Medical College, Attending Neurologist, New York Hospital.*)

Effect of Aspirin Dosage on Stroke Risk in Women

ABSTRACT & COMMENTARY

Source: Iso H, et al. Prospective study of aspirin use and risk of stroke in women. *Stroke* 1999;30:1764-1771.

Several randomized clinical trials have established the benefit of low-dose aspirin in the secondary prevention of ischemic stroke in both men and women (The SALT Collaborative Group. *Lancet* 1991; 338:1345-1349; Drener HC, et al. *J Neurol Sci* 1996; 143:1-13; UK-TIA Study Group. *J Neurol Neurosurg Psychiatry* 1991;54:1044-1054). The role of aspirin in primary prevention of stroke is uncertain, especially in women. Two trials in men were inconclusive but suggested a possible excess risk of disabling stroke (Peto R, et al. *BMJ* 1988;296:313-316) or cerebral hemorrhage (The Steering Committee of the Physicians' Health Study Research Group. *N Engl J Med* 1989;321:129-135) in the aspirin group.

Iso and colleagues previously analyzed six years' prospective data from the Nurses' Health Study (Manson JE, et al. *JAMA* 1991;266:521-527) and found no significant relation between aspirin use and the risk of ischemic or hemorrhagic stroke. In the present study, they report on 14 years' follow-up in the Nurses' Health Study cohort. The number of incident strokes (n = 503, 295 ischemic, 100 subarachnoid hemorrhages, 52 intraparenchymal hemorrhages, and 56 type undetermined) permitted a reinvestigation of the relation of aspirin use to stroke subtypes. The participants were classified into

five groups of aspirin use as reported on questionnaires in 1980, 1982, 1984, and 1988 (*see Table*). Women who took 1-6 aspirin per week had a lower risk of large-artery occlusive infarction than women who took no aspirin; the multivariate relative risk was 0.50 (95% CI 0.29-0.85; P = 0.01). The reduction was of greater magnitude for older, hypertensive, or smoking women than for younger, nonhypertensive, or nonsmoking women.

In contrast, women who took 15 or more aspirin per week had a two-fold excess risk of subarachnoid hemorrhage (SAH), the multivariate relative risk was 2.02. The elevation in SAH with aspirin was more apparent for older or hypertensive women than for younger or nonhypertensive women. Aspirin use was not associated with risk of other subtypes of stroke, such as embolic or lacunar infarction.

Table

Strokes in 79,319 Women From 1980-1994, According to Aspirin Use

	Aspirin Per Week, n				
	0	1-2	3-6	7-14	≥ 15
Women, n	19,233	24,702	11,258	7900	4694
All Strokes	201	114	60	87	41
Ischemic Strokes	118	74	34	52	17
Embolic Infarcts	12	10	4	5	2
Large Artery Occlusive Infarction	41	15	7	15	4
Lacunar Stroke	48	35	18	31	8
Hemorrhagic Stroke	61	31	22	22	16
Subarachnoid Hemorrhage	37	23	15	13	12

COMMENTARY

This observational study in middle-aged women found that the effect of aspirin varied according to the dosage. The regular intake of 15 or more aspirin weekly increased the risk of SAH. SAH is the only subtype of stroke that is more prevalent in women than in men. The excess risk of SAH in women taking large amounts of aspirin was two-fold over all, and three-fold among older and hypertensive women. Iso et al speculate that high-dose aspirin, by producing a combined inhibitory effect on both the synthesis of thromboxane A2 in platelets and of prostacyclin in vascular endothelial cells, leads to an increased bleeding tendency and to vasospasm, respectively. Iso et al postulate that spasm in cerebral arteries may increase hemodynamic stress at vulnerable sites for the development and rupture of saccular aneurysms.

In contrast, the weekly intake of 1-6 aspirins reduced the risk of large artery occlusive infarction. Extrapolation of these data to men seems warranted and, therefore, physicians are justified in recommending daily low-dose aspirin to their patients of either sex for the prevention of atherothrombotic stroke. Likewise, the chronic, excessive use of aspirin for the treatment of arthritis and headaches should be avoided. **—jjc**

Cluster Headache: Origins and Treatment

ABSTRACTS & COMMENTARY

Sources: May A, et al. Correlation between structural and functional changes in brain in an idiopathic headache syndrome. *Nat Med* 1999;5:836-838; Goadsby PJ, et al. Oral zolmitriptan is effective in the acute treatment of episodic cluster headache. *Neurology* 1999;52:A257, Abst S32.006.

Present dictum states that migraine mechanisms and symptoms originate in the central nervous system, either central, peripheral, or both. Most neurologists have considered cluster headaches as belonging to the migraine family. Until now, however, despite their 90% predilection in males, their agonizing pain, their short, 1-2 hour duration, their predictable cholinergic expressions of Horner syndrome, copious lachrymation, rhinorrhea, and facial sweating, their clock-like outbursts during cluster periods, and the long periods that sometimes separate their outbursts, little has been learned about the fundamental biology of cluster headaches or, much less, their relationships to migraine. Nor has any present-day expert on the disease attributed the pain of cluster headache to peripheral neural receptor systems. Three recent communications, however, have now begun to identify unique changes that appear during and between times of active cluster headaches. The first two report on functional and anatomical changes that are apparently unique within the brains of patients suffering from cluster headache. In the third, Goadsby and colleagues comment that zolmitriptan, a variant anti-migraine drug, relieves about 40% of patients with episodic, but not chronic, cluster headaches.

A little more than a year ago, May and associates (May A, et al. *Lancet* 1998;351:275-278) published the first report to identify specific, functional brain regions associated with cluster headaches. (*Neurology Alert* apologizes for letting this go by.) Headaches identical to the spontaneous cluster head pains, including the cholinergic side

effects, were induced by inhaled nitroglycerin (this maneuver produces no headache in normals). In response, the susceptible men developed not only the usual expected functional areas creating or reacting from pain, but also revealed unpredicted, high, specific diencephalic activity in the posterior hypothalmus ipsilateral to the headache. For the first time, a specific relation of vascular headache to a functional area of the brain had been discovered.

As emphasized in the *Nature Medicine* report, further experimentation identified increased functional brain activity in both hypothalamic areas, but remained greater on the headache side both during headaches and in their absence. The explanation of such "neuronal increase," its duration and its durability remains to be evaluated. Furthermore, May et al have identified significant anatomic increases in bilateral gray matter density surrounding the hypothalamic zones of the headache cluster patients. May et al infer that these areas contain increased neurons packed tightly in the two regions, creating a specific "previously unrecognized abnormality in the hypothalamic region." Age did not affect the consistent findings but, as is well known, males expressed at least 90% of the total cases. This lack of difference implies a consistent, continuous functional change in the hypothalamus of patients with cluster headache.

COMMENTARY

This important and ingenious study leaves both patient and doctor wondering about the exact neurologic functions that pull the hypothalamic trigger in the cluster-susceptible brain. May et al emphasize, somewhat tangentially, that the sleep/wake pattern reminds one of the hypothalamic regulation of normal circadian sleep/wake cycles. It is hard to overlook the clock-like repetitions of these headache patterns as they come relatively regularly both night and day. Nevertheless, one cannot immediately associate them with consistent patterned activity generated by hypothalamic circadian functions. For one thing, and fortunately for cluster patients, what in the basal hypothalamic supra-optic time-clock would generously permit the headache signal to turn off for months at a time? Only circadian sleep or hormonal studies may presently more greatly relate the expressions of active cluster to other hypothalamic activities. One can't help thinking of the seasonal and daily periods of clusters that characterize peripherally generated, classic trigeminal neuralgia (TN), with or without the putative trauma of possible cerebellar artery pulsations beating on the peripheral branches. TN also has a tendency to appear day or night in spring or fall, but the epidemiology of onset and times of the clock have not been abundantly analyzed. Also, TN more frequently affects persons older than 55 years of age and may suddenly, spontaneously cease for as much as years between episodes. And so it goes for clinical neuroscience: we'll never solve all its questions, we only can try. **—fp**

Vascular Dementia: Patterns and Protection by Antihypertensive Drugs

ABSTRACTS & COMMENTARY

Sources: Looi JC, Sachdef PS. Differentiation of vascular dementia from AD on neuropsychological tests. *Neurology* 1999;53:670-678; Guo Z, et al. Occurrence and progression of dementia in a community population aged 75 years and older. Relationship of antihypertensive medication use. *Arch Neurol* 1999;56:991-996.

Looi and sachdef extracted a meta-analysis of 27 acceptable studies on vascular dementia (VaD) directed at the above title. These, and a larger number of anecdotal references, provide a number of clinical factors that may help to separate these diagnoses, although many experienced neurologists already recognize the difference in at least the advanced forms of either.

Fundamentally, Alzheimer's disease (AD) undergoes an insidious but steadily progressive evolution, beginning mostly after 70 years of age. Often, the victim has one or more family members with similar memory losses. Short-term, episodic, verbal-event memory usually undergoes an early loss, followed by defects in semantic memory and eventually, long-term memory loss as well. Language degenerates, morsel by morsel, often developing into a progressive, general aphasia in later years. Motor dysfunction, if any, usually occurs late in the disease. Potential markers are the E3-4 alleles of the serum lipoproteins and an MRI brain scan that shows neither a large number of scattered white patches in the hemisphere nor consistently large ventricles. Hippocampal shrinkage may be defined by MRI in relatively late stages of the illness.

VaD occurs at roughly the same age or even younger than AD and usually develops one or more of four relatively consistent markers: similar VaD ancestral cases, but less consistently than with AD; a long history of even modest hypertension or other lipid-related arterial diseases; frontal lobe dysfunction in executive activities; and, early during the illness, a waxing and waning of memory as well as intentionality in behavior. As noted

above, MRI scanning usually defines multiple small and sometimes large demyelinated spots, mostly in the cerebrum, but consistent with focal ischemia, cerebral ventricular dilatation often occurs. Persons with vascular dementia tend to retain better language qualities than AD during the middle to late years of their problems. Many wander in and out of confusion, becoming incontinent and unsteady on their feet during the late stages.

Against the above background, Guo and colleagues describe a somewhat unexpected success in adding antihypertensive medication to the elderly dementia protection list.

Guo et al selected 1810 patients older than 74 years from the Stockholm area to conduct a dementia incidence study; 225 already had dementia, a prevalence of 12.4% at the time the study began. An additional 284 persons refused initial testing. This left 1307 without dementia for further testing after two years. Before the end of the two-year follow-up, 314 of the 1307 died, leaving 987 persons for detailed evaluation after 24 months. At the time of baseline assembly, subjects already taking diuretics with or without additional antihypertensive drugs had a higher score on the MMSE ($P = 0.006$) and a lower prevalence of dementia ($P < 0.004$). At the end of the two-year follow-up time another 199 of the baseline 987 had become demented (20%). Also, among a total of 314 deaths occurring before the full two years, 25 had become demented (8%). Overall, subjects taking antihypertension drugs had significantly less dementia than the remaining patients ($P = 0.03$).

Diuretics and other antihypertensive agents were taken by 484 persons at baseline. Despite the fact that they were a bit older and had more heart disease and stroke than persons not using antihypertensive drugs, the population receiving the drugs had significantly ($P < 03$) less dementia than did the remaining senescents.

In the 987 persons retested at two years (excluding deaths), subjects taking diuretics had an adjusted risk rate (RR) of 0.7 compared to the remaining population. Put another way, subjects not taking antihypertensive drugs declined into dementia at a rate of 17% per year. Persons taking the diuretics with or without other antihypertension agents had less than half that chance of becoming demented.

COMMENTARY

Looi and Sachdef crystallize the major four clinical markers (exclusive of MRI film results) that best characterize the presence of cerebral-vascular dementia. As they emphasize, indicants of possible VaD should lead to suspicion of impaired clinical function but they lack firm, high probability. AD, on the other hand, by its absence of frontal lobe dysfunction and early characteristics of impaired short-term memory plus fractured language abilities, usually clinically characterizes itself. Identification of serum lipoprotein alleles E3 and/or E4 considerably increases the accuracy of diagnosing AD. As the following paragraph indicates, cerebral arterial sclerosis may have a lighter, treatable incidence than has previously been surmised.

Guo et al's report expresses a major point, namely that even mild systemic hypertension apparently can independently cause dementia or accelerate the destruction resulting from several degenerative neurological illnesses. The message is clear: neurologists treating patients of any age who develop blood pressure greater than 150/85-90 mmHg should consider prescribing permanent treatment with a diuretic or equivalent antihypertensive drug. AD, however, is not to be ignored as a subtle, additional factor to vascular dementia. First of all, the disease has no inexpensive laboratory tests that firmly identify the illness, and second, your editor knows of laboratory animal experiments that have found that cholinergic stimulants such as donepezil may improve the behavior of laboratory rodents following experimental obstruction of cerebral arteries. **—fp**

Antiplatelet Treatment Does not Reduce the Severity of Subsequent Stroke

ABSTRACT & COMMENTARY

Source: Sivenius J, et al. Antiplatelet treatment does not reduce the severity of subsequent stroke. European Stroke Prevention Study 2 Working Group. *Neurology* 1999;53: 825-829.

The european stroke prevention study (esps) published in 1996 demonstrated the benefit of a combination of aspirin and dipyridamole (twice daily 25 mg aspirin with 200 mg slow-release dipyridamole) over either agent alone or placebo (Diener HC, et al. *J Neurol Sci* 1996;143:1-13). The combination regime produced a 37% risk reduction for stroke, compared to 18% for aspirin alone. Sivenius and colleagues now present an analysis of 701 patients with stroke during two-year follow-up of the original 6602 patients in the ESPS2 cohort. Using the Rankin outcome scale, there was no difference in stroke severity among the four groups studied. This disability

score measures the important outcome of functional status, but is not sensitive to neurologic subtleties such as dysphasia or a visual field defect. In keeping with the original results of the ESPS2 study, time to recurrent stroke was longest in the group that received combination therapy.

COMMENTARY

In vitro evidence has suggested that aspirin may exert a neuroprotective effect independent of its antithrombotic properties (Grilli M, et al. *Science* 1996;274:1383-1385). In clinical trials, however, stroke has been shown to be equally severe among patients on a range of aspirin doses (100-500 mg) or on no prior aspirin therapy (Karcpov V, et al. *Arch Neurol* 1997;54:1369-1371). The current analysis by Sivenius et al further supports this. Aspirin and other antiplatelet agents remain the mainstay of stroke prophylaxis. However, when these agents fail, the size of the thrombus and extent of ischemic damage are likely the same, regardless of prior therapy. **—azs**

Attention CME Subscribers

CME question no. 21 in the October 1999 issue of *Neurology Alert* should have been question no. 20. We regret any confusion this may have caused. ❖

CME Questions

21. Which one of the following statements regarding deep brain stimulation for dystonia is true?

a. Deep brain stimulation of the globus pallidus improves blepharospasm and torticollis but does not improve truncal dystonia.
b. The effect of the deep brain stimulator is maximal immediately after implantation.
c. Deep brain stimulation of the globus pallidus increases activation of the motor and supplementary motor cortex when the patient performs a motor task.
d. The surgical risk of hemmorhage, stroke, or blindness from implantation of a stimulator is 1-2%.

22. In women, aspirin is affected by which type of stroke risk?

a. Embolic stroke
b. Lacunar infarcts
c. Large artery occlusive infarcts
d. Subarachnoid hemorrhage
e. Cerebral (parenchymal) hemorrhage

Annual Statement of Ownership, Management, and Circulation

United States Postal Service
Statement of Ownership, Management, and Circulation

1. Publication Title	2. Publication No.	3. Filing Date
Neurology Alert	0 7 4 1 - 4 2 3 4	9/24/99
4. Issue Frequency	5. Number of Issues Published Annually	6. Annual Subscription Price
Monthly	12	$209.00

7. Complete Mailing Address of Known Office of Publication *(Not Printer) (Street, city, county, state, and ZIP+4)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, Fulton County, GA 30305 — Contact Person: Willie Redmond — Telephone: 404/262-5448

8. Complete Mailing Address of Headquarters or General Business Office of Publisher *(Not Printer)*: 3525 Piedmont Road, Bldg. 6, Ste. 400, Atlanta, GA 30305

9. Full Names and Complete Mailing Addresses of Publisher, Editor, and Managing Editor *(Do Not Leave Blank)*

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Editor *(Name and Complete Mailing Address)*: Neill Larmore, same as above

Managing Editor *(Name and Complete Mailing Address)*: Glen Harris, same as above

10. Owner *(Do not leave blank. If the publication is owned by a corporation, give the name and address of the corporation immediately followed by the names and addresses of all stockholders owning or holding 1 percent or more of the total amount of stock. If not owned by a corporation, give the names and addresses of the individual owners. If owned by a partnership or other unincorporated firm, give its name and address as well as those of each individual. If the publication is published by a nonprofit organization, give its name and address.)*

Full Name	Complete Mailing Address
American Health Consultants	3525 Piedmont Road, Bldg. 6, Ste 400 Atlanta, GA 30305

11. Known Bondholders, Mortgagees, and Other Security Holders Owning or Holding 1 Percent or More of Total Amount of Bonds, Mortgages, or Other Securities. If none, check box → ☐ None

Full Name	Complete Mailing Address
Medical Economics Data, Inc.	Five Paragon Drive Montvale, NJ 07645

12. Tax Status *(For completion by nonprofit organizations authorized to mail at nonprofit rates.) (Check one)*
The purpose, function, and nonprofit status of this organization and the exempt status for federal income tax purposes:
☐ Has Not Changed During Preceding 12 Months
☐ Has Changed During Preceding 12 Months *(Publisher must submit explanation of change with this statement)*

PS Form **3526**, September 1998 *See instructions on Reverse)*

13. Publication Name: Neurology Alert — 14. Issue Date for Circulation Data Below: November 1999

15. Extent and Nature of Circulation			Average No. of Copies Each Issue During Preceding 12 Months	Actual No. Copies of Single Issue Published Nearest to Filing Date
a. Total No. Copies *(Net Press Run)*			2761	2640
b. Paid and/or Requested Circulation	(1)	Paid/Requested Outside-County Mail Subscriptions Stated on Form 3541. *(Include advertiser's proof and exchange copies)*	2523	2390
	(2)	Paid In-County Subscriptions *(Include advertiser's proof and exchange copies)*	0	0
	(3)	Sales Through Dealers and Carriers, Street Vendors, Counter Sales, and Other Non-USPS Paid Distribution	0	0
	(4)	Other Classes Mailed Through the USPS	0	0
c. Total Paid and/or Requested Circulation *(Sum of 15b(1) and 15b(2)*			2523	2390
d. Free Distribution by Mail *(Samples, Complimentary and Other Free)*	(1)	Outside-County as Stated on Form 3541	0	0
	(2)	In-County as Stated on Form 3541	0	0
	(3)	Other Classes Mailed Through the USPS	0	0
e. Free Distribution Outside the Mail *(Carriers or Other Means)*			18	18
f. Total Free Distribution *(Sum of 15d and 15e)*			18	18
g. Total Distribution *(Sum of 15c and 15f)*			2541	2408
h. Copies Not Distributed			220	232
i. Total *(Sum of 15g, and h.*			2761	2640
Percent Paid and/or Requested Circulation *(15c divided by 15g times 100)*			99	99

16. Publication of Statement of Ownership
Publication required. Will be printed in the November issue of this publication. ☐ Publication not required.

17. Signature and Title of Editor, Publisher, Business Manager, or Owner: Publisher — Date: 9/24/99

I certify that all information furnished on this form is true and complete. I understand that anyone who furnishes false or misleading information on this form or who omits material or information requested on the form may be subject to criminal sanctions (including fines and imprisonment) and/or civil sanctions (including multiple damages and civil penalties).

Instructions to Publishers

1. Complete and file one copy of this form with your postmaster annually on or before October 1. Keep a copy of the completed form for your records.
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PS Form **3526**, September 1999 *(Reverse)*

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