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A monthly survey of developments in neurologic medicine

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Will New Approaches Help to Treat ALS?

ABSTRACT & COMMENTARY

Source: Almer G, et al. Increased levels of the pro-inflammatory prostaglandin PGE2 in CSF from ALS patients. *Neurology.* 2002;58: 1277-1279.

Inflammatory mechanisms may participate in the pathogenesis of neurodegenerative diseases including ALS. It has been known for many years that there is a problem with neuroinflammatory reaction in ALS. The classic findings are those of activated microglia that express high levels of a number of inflammatory molecules such as CD11b.

Several recent studies have directly implicated cyclooxygenase 2 (COX-2) activity in ALS pathogenesis. It was initially shown that there was a dramatic increase in COX-2 activity in postmortem spinal cord samples from sporadic ALS patients (Yasojima K, et al. *Neurology.* 2001;57:952-956). This was demonstrated by measuring prostaglandin PGE2 levels, which are a known product of COX-2. Subsequent work on ALS spinal cord showed a 7-fold upregulation of COX-2 mRNA and a 3.8-fold increase in protein levels (Almer G, et al. *Ann Neurol.* 2001;49:176-185). The most recent study has examined PGE2 levels in cerebrospinal fluid of ALS patients. It was demonstrated that 82% of the patients had levels that were 2-10-fold higher than levels in normal control subjects.

Editor's Note—*In this issue of Neurology Alert, Flint Beal, MD, will join me as the co-editor. Dr. Beal is Professor and Chairman of the Department of Neurology at Cornell University Medical College. During my 20 years of editorship, the goal of Neurology Alert has been to present clinicians with the latest information, especially when new treatments appear that will better ameliorate severe disorders. Neuroscience, both fundamental and clinical, now faces the greatest changes of all clinical disciplines, demanding rapid exploration, understanding, and biological treatment. Neurology Alert will continue presenting the most current information to assist the well-informed clinical neurologist.* —***Fred Plum, MD***

VOLUME 21 • NUMBER 1 • SEPTEMBER 2002 • PAGES 1-8

INSIDE

Highlights from the 8th ICADRD meeting **page 2**

Preclinical Huntington's disease **page 3**

Hyperglycemia and the acute ischemic penumbra **page 4**

Celiac disease **page 5**

Is NPH a valid concept? **page 6**

Ischemic white matter disease **page 7**

COMMENTARY

These findings raise the possibility that the administration of COX-2 inhibitors, which are well tolerated in man, could prove to be a useful therapeutic strategy for ALS. Consistent with this, COX-2 inhibitors were shown to protect organotypic spinal cord cultures from glutamate toxicity. Furthermore, the COX-2 inhibitor celecoxib (Celebrex®) has been shown to significantly extend survival in a transgenic mouse model of ALS that expresses the mutant form of superoxide dismutase that is associated with human ALS (reported at last year's ANA meeting). In these mice, it has also been demonstrated that there is a marked increase in expression of COX-2, which is seen not only in glial cells but also in the spinal cord anterior horn neurons. There is also substantial other evidence from gene profiling indicating that inflammatory mechanisms may play an important role in this transgenic mouse model of ALS. These findings are preliminary and deserve replication. Nevertheless, the results, when viewed in concert, are very provocative and suggest that COX-2 inhibitors might be useful in slowing the progress of this otherwise devastating illness. In view of this, initial clinical trials are underway using the selective COX-2 inhibitor celecoxib. **—M. FLINT BEAL**

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Highlights from the 8th Annual International Alzheimer's Disease Meeting

CONFERENCE COVERAGE

Source: *Neurobiol Aging.* 2002;23(1S):S1-S606.

MORE THAN 2000 DEMENTIA-RELATED STUDIES were presented at the 8th International Conference on Alzheimer's Disease and Related Disorders (ICADRD), held in Stockholm, Sweden, July 20-25, 2002. Several items of potential interest to neurologists bear mention.

If there were such a title, cholesterol would probably have been voted "Molecule of the Year" at the 2002 ICADRD meeting, based on the sheer number of presentations concerning the cholesterol-lowering statins as a potential means of treating Alzheimer's disease (AD).

Two years ago, 2 retrospective epidemiologic studies suggested that use of statins might reduce the risk of AD as much as 40-79% (Wolozin B, et al. *Arch Neurol.* 2000;57:1439; Jick H. *Lancet.* 2000;356:1627). Two new epidemiologic studies presented at the ICADRD lend further support to this idea. A retrospective study from Boston University carried out on 2378 individuals from Alzheimer-affected families, including 547 African Americans, found reduced risk of AD among statin users regardless of their APOE genotype, race, or the brand of statin prescribed. Another study examined 4740 residents of Cache County, Utah, older than 65 years and found that statin use was associated with a reduced prevalence of dementia but had no statistically significant effect on AD incidence. In addition, use of statins that penetrated the blood brain barrier was associated with less risk reduction than use of agents that did not enter the brain, such as atorvastatin (Lipitor®). This is the first substantive study to find that statin use inversely correlated with the prevalence, but not incidence, of AD, and the first to indicate possible differences among available statins in lowering risk of AD. Other presentations at the ICADRD provided evidence that cholesterol can influence the pathophysiology of AD and suggested mechanisms whereby statins might exert their protective effects. While these developments are encouraging, prospective verification of AD risk reduction by statins has yet to be carried out. However tempting this may seem, it is premature to consider prescribing statins for the sole purpose of preventing or treating dementia until prospective tests are completed.

Another topic that received considerable attention at

the ICADRD meeting was the identification of prognostically relevant subgroups among patients with mild cognitive impairment (MCI). Patients with MCI have memory or other cognitive impairments that are greater than most people their age, but are not sufficiently impaired functionally to be considered demented. MCI patients are at increased risk for development of dementia, with an estimated 10-15% progressing to diseases such as AD each year. Several studies have now indicated that the MCI population is heterogeneous, and not all patients with MCI have the same level of risk for developing AD. The emerging consensus is that most patients with MCI will go on to develop dementia within 10 years, but not all will develop AD. It is now recognized that subgroups of MCI patients can be distinguished that have the highest likelihood of developing AD. Unfortunately, there is still a great deal of variability across studies in defining these MCI subtypes. "Amnestic MCI" and "MCI-AD" are 2 such characterizations of MCI patients that attempt to identify a greater likelihood of developing AD based on the characteristics of the cognitive impairments. Definitional issues and the difficulties involved in testing for the relatively subtle cognitive deficits associated with MCI are likely to limit the clinical application of the MCI construct for the time being. Once these issues have been overcome in the future, identification of MCI and its subtypes is likely to become an important part of the strategies used for the early detection and prevention of AD.

Acetylcholinesterase inhibitors were the subject of some discussion at the ICADRD conference. Head-to-head comparisons of the available agents revealed distinctions among donepezil, rivastigmine, and galantamine in terms of their ease of use and tolerability, but less clear differences in their efficacy. Broadened use of these agents in treating other forms of dementia can be anticipated based on the results of studies using galantamine and donepezil in patients with vascular dementia and mixed dementias. The results reported at the ICADRD suggested short-term (6 month) symptomatic benefits in treating patients with vascular dementia. The long-term benefits have yet to be determined, and as yet, none of the cholinesterase inhibitors have received FDA approval for this indication.

Acetylcholinesterase inhibitors are the mainstay of therapy for AD throughout the world, but several new classes of medicines are under development. Among the latter group, the selective NMDA antagonist Memantine shows promise, both in terms of its efficacy in treating severe dementia and its track record of tolerability. Memantine has been approved for treatment of dementia in Germany for over a decade, and it is currently in Phase 3 clinical trials in the United States. The glutaminergic mechanism of action of memantine is distinct from that of other currently approved treatments. At least one study presented at the ICADRD suggested that memantine can be safely administered in combination with acetylcholinesterase inhibitors. Barring unexpected results in ongoing clinical trials, memantine appears to have reasonable prospects for future approval in the United States as a symptomatic treatment for AD.

Looking to the future, one of the most exciting developments in AD therapeutics is the advent of techniques for manipulating beta-amyloid production and deposition in the brain. The use of immunotherapy against amyloid suffered a setback this past year when several patients in the Elan AN1792 trial developed brain inflammation. Nevertheless, immunotherapy is still considered to be a viable approach, although modifications to the active immunization strategy used by the Elan trial will be needed. Another interesting approach involves the development of small molecules that can sequester amyloid in the periphery, thereby creating a gradient for movement of amyloid out of the brain. Animal studies suggest the feasibility of this approach, and clinical trials are anticipated in the near future. The development of inhibitors targeting the amyloid-producing secretase enzymes is also moving forward, although no efficacy data from human trials have been formally presented as yet. With the multiplicity of agents designed to alter amyloid burden now in the pipeline, new brain imaging methods are needed to measure amyloid burden in living brain. Techniques currently under development use radioligands or MRI contrast labels to bind plaques in human brain. While it may be several years before amyloid imaging and amyloid-based treatments become part of routine clinical practice, these developments suggest that a new era in AD diagnosis and treatment is now getting underway. **—NORMAN R. RELKIN**

Structural Neuropathology in Preclinical Huntington's Disease

ABSTRACT & COMMENTARY

Source: Thieben MJ, et al. The distribution of structural neuropathology in preclinical Huntington's disease. *Brain.* 2002;125:1815-1828.

HUNTINGTON'S DISEASE (HD) IS AN AUTOSOMAL dominant neurodegerative disorder linked to an

expanded CAG trinucleotide repeat within the IT15 gene located on chromosome 4. Classical past neuropathologic descriptions of HD emphasized the predilection for involvement of the striatum, particularly the head of the caudate and putamen. Much emphasis was placed on clinical correlation between the degree of striatal pathology and symptoms of chorea and cognitive disturbance. Recently, it has become clear that this view of HD as a disease limited to the basal ganglia is incorrect, grossly underestimating the widespread neuropathologic changes that characterize the disorder. Prior therapeutic approaches have targeted the basal ganglia, for example, transplanting embryonic cells into caudate or putamen, with disappointing results. In order to rationally design therapies that will impact the natural history of this degenerative disorder, it is critical to understand the sequence and distribution of pathologic changes in the brains of HD patients.

In this seminal study, Thieben and colleagues set out to define the structural neuropathology in preclinical HD. Using a population of individuals who had undergone predictive genetic testing, 12 subjects were selected with more than 40 CAG repeats (guaranteeing eventual development of HD), and 5 had between 36 and 39 repeats (at risk for developing HD). A neurologist who was blinded to patients' genetic status evaluated all patients, and none had evidence of HD on exam. Whole-brain MRIs and voxel-based morphometry were performed using statistical parametric mapping. The advantage of this technique is that it is fully automated and does not rely on region of interest evaluations (which introduce the possibility of investigator bias). Thieben et al observed significant reductions in grey matter volume in the left head and body of the caudate, putamen, and globus pallidus, continuous with volume loss in the nucleus accumbens and orbito-frontal cortex. Volume loss on the right side in the striatum was not statistically significant. They also observed grey matter loss in the tectum of the brainstem, posterior insula and posterior intra-parietal sulcus, and bilateral reduction in periventricular white matter volume in frontal, occipital, and temporal horns of the lateral ventricles.

COMMENTARY

Several interesting and important conclusions can be drawn from this study. Early involvement of the striatum is not surprising given the noted predilection for this structure. However, the asymmetry of involvement was a surprise. Further, striatal volume loss was most severe rostrally and ventrally, in apparent contradiction to previous serial autopsy studies of HD brains. Involvement of the other brain regions correlates well with early clinical features of the illness. Bilateral volume loss of the insular cortex may explain the early loss of facial recognition characteristic of HD patients. Involvement of the intra-parietal sulcus and midbrain tectum may explain the delay in initiation of voluntary saccades that is frequently seen early in the disorder. The unexpected widespread white matter changes preceding clinical symptoms further confirms the idea that the brains of HD carriers are grossly and widely abnormal. Also, they appear well before they show symptoms and signs of the disease. This study suggests that future therapeutic approaches of HD must target all areas of the brain, almost certainly by pharmacologic agents that affect the bioenergetic disturbance underlying this presently untreatable neurodegenerative disorder. **—STEVEN FRUCHT**

Hyperglycemia and the Acute Ischemic Penumbra

ABSTRACTS & COMMENTARY

Sources: Parsons MW, et al. Acute hyperglycemia adversely affects stroke outcome: A magnetic resonance imaging and spectroscopic study. *Ann Neurol.* 2002;52:20-28; Ginsberg MD. Hyperglycemia and stroke outcome: Vindication of the ischemic penumbra. *Ann Neurol.* 2002;52:5-6.

Over the past 25 years, many experimental studies and clinical surveys of acute ischemic stroke have confirmed the observation of Myers and Yamaguchi (Myers RE, Yamaguchi S. *Arch Neurol.* 1977;34:65-74) that elevated plasma glucose levels coincident with acute ischemia are associated with a worse outcome.

The senior editor of *Neurology Alert* and his collaborators, among others, previously reported that hyperglycemia augments ischemic brain damage in rats (Pulsinelli WA, et al. *Neurology.* 1982;32:1239-1246) and in acute stroke patients whether or not they had established diabetes mellitus (Pulsinelli WA, et al. *Am J Med.* 1983;74:540-544).

The postulated mechanism of neuronal injury is that during ischemia, elevated brain glucose levels in conjunction with an ischemia-induced shift to anaerobic glycolysis lead to severe tissue lactic acidosis which, in turn, leads to tissue necrosis. Therefore, one would predict that hypoperfused brain tissue or the acute ischemic penumbra should produce increased levels of lactic acid during hyperglycemia because of ongoing delivery of glucose to

ischemic tissue capable only of anaerobic metabolism.

Studies in humans prior to the advent of magnetic resonance imaging (MRI) were unable to establish that hyperglycemia in acute ischemic stroke promotes the infarction of hypoperfused but potentially viable brain tissue. At present, MRI with perfusion-weighted imaging (PWI), diffusion weighted imaging (DWI), and MR spectroscopy provide the means to examine the relationship between hyperglycemia and infarction in humans.

Patients imaged at the hyperacute stage of stoke typically demonstrate PWI > DWI lesion mismatch which the authors have postulated to be the MRI image of the penumbra (Barber PA, et al. *Neurology.* 1988;51:418-426). During the first 24 hours after stroke onset, some of the PWI lesion becomes DWI positive and the rest of the PWI area contracts due to reperfusion and tissue salvage. MR spectroscopy detects both the presence of lactate in brain tissue within minutes of the onset of cerebral ischemia, and serial increases in lactate levels when ongoing ischemia leads to continuing lactate production (Parsons MW, et al. *Neurology.* 2000;55:498-505).

Parsons et al performed prospective serial PWI, DWI, MR spectroscopy, and blood glucose studies in 63 acute stroke patients. The presence of acute PWI > DWI mismatch was used to identify hypoperfused at risk of infarction tissue or penumbra. In 40 of 63 patients with acute PWI > DWI mismatch, acute hyperglycemia was correlated with reduced salvage of penumbra from infarction, greater final infarct size, and worse functional outcome. There was a strong independent relationship between increasing acute blood glucose and reduced penumbral salvage such that a doubling of blood glucose from 5 to 10 mm/L led to a 60% reduction in penumbral salvage.

Higher acute blood glucose in patients with PWI > DWI mismatch was associated with greater lactate production. This also was independently associated with reduced salvage of at-risk tissue. In nonmismatch patients (PWI = DWI) without an ischemic penumbra, acute blood glucose levels did not correlate with outcome nor was there any increasing lactate production in this group. Therefore, as pointed out by Ginsberg in his editorial, these results establish that the deleterious influence of acute hyperglycemia is on penumbral tissue and is reflected in increased acute tissue lactate production.

COMMENTARY

Although some clinical studies have concluded that hyperglycemia adversely affects the outcome of acute ischemic stroke, others have not found it to be an independent risk factor but rather an epi phenomenon or marker of a catecholamine-mediated stress response to a more severe stroke (Tracey F, Stout RQ. *Stroke.* 1994; 25:524-525). The study of Parsons et al further establishes the clinical danger of hyperglycemia and defines both the probable mechanism of injury by means of lactic acidosis and the site of action as the ischemic penumbra. The ischemic penumbra as defined by Ginsberg is "a hypoperfused, clinically and metabolically unstable tissue region potentially at risk of irreversible injury, yet capable of salvage in response to acute measures taken to increase perfusion and/or confer metabolic neuroprotection."

Hyperglycemia in acute stroke appears to deserve aggressive management that must be initiated as soon as possible, that is, within the same "therapeutic window" as thrombolytic treatment. The practical implementation of acute measures to reduce elevated blood glucose levels requires care lest over aggressive treatment produce even more deleterious hypoglycemia. **—JOHN J. CARONNA**

Neurology of Celiac Disease

ABSTRACT & COMMENTARY

Source: Tengah DS, et al. Neurological complications of celiac disease. *Postgrad Med J.* 2002;78:393-398.

BEST RECOGNIZED AS A CHRONIC DIARRHEAL ILLNESS with bloating and progressive weight loss, celiac disease has a definite association with a number of conditions including dermatitis herpetiformis, IgA deficiency, IgA nephropathy, Sjogren's syndrome, autoimmune thyroid disease, Type 1 diabetes, rheumatoid arthritis, and Down's syndrome. Gastrointestinal carcinoma or lymphoma occurs in up to 15% of refractory or untreated cases. Less commonly associated are several neurological disorders that may occur in up to 10% of patients.

Among 620 patients with celiac disease, 189 (30%) had a neurologic condition, but any causal relationship remained uncertain. Depression (11.5%), epilepsy (4.0%), and migraine (3.2%) were most common, followed by carpal tunnel syndrome and stroke (2.4% each). Spinocerebellar ataxia has been reported in celiac disease but was not seen in this group and an association between celiac disease, antigliadin, antireticulin, or antiendomysial antibodies and cerebellar disorders remains doubtful. Epilepsy is associated with one variant of celiac disease, curiously combined with bilateral occipital calcifications, the latter only in Italians. Folate deficiency may play a role in this syndrome. Peripheral neuropathy was seen in 0.5% (3/620) but does not always respond to a gluten-free diet. Similarly, no definite association exists with multiple sclerosis, Parkin-

son's disease, or dementia.

Nutritional deficiency may play a role in the neurologic complications of celiac disease but, again, a causal association remains weak. B6 (pyridoxine) coupled with a gluten-free diet improved depression after 3 years (*Scand J Gastroenterol.* 1983;18:299-304) and vitamin E replacement reportedly improved ataxia associated with celiac disease (*Lancet.* 1996;347:446). Deficiency of B12, biopterin, or carnitine and causality for any neurologic condition in celiac disease remains to be proven. Altered autoimmunity and gluten neurotoxicity are etiologic hypotheses in search of evidence.

COMMENTARY

Celiac disease affects 1 in 300 persons of European descent in North America but is rare in blacks and Asians. HLA-DQ2 is expressed in more than 95% of patients with this gluten enteropathy. The disease is induced, in susceptible persons, by food-grain antigens in wheat, barley, and rye. Ingested antigen, toxic amino acid sequences in a-gliadin, induces an inappropriate T-cell mediated immune response when HLA-DQ2 presents the antigen to stimulate intestinal mucosal T cells. Adherence to a gluten-free diet prevents all the disease complications, and early diagnosis is important. Serologic screening for antigliadin antibodies is 90% sensitive but nonspecific, whereas sensitivity and specificity for positive IgA antiendomysial antibodies approaches 98% and 100%, respectively. Small bowel biopsy remains the gold standard. Antibody positivity disappears after 6 months of initiating a gluten-free diet and is useful to monitor compliance. **—MICHAEL RUBIN**

Is Normal Pressure Hydrocephalus a Valid Concept in 2002?

ABSTRACT & COMMENTARY

Source: Bret P, et al. Is normal pressure hydrocephalus a valid concept in 2002? A reappraisal in five questions and proposal for a new designation of the syndrome as "chronic hydrocephalus." *J Neurol Neurosurg Psychiatry.* 2002; 73:9-12.

1. Was NPH actually a newly discovered condition when reported by Adams, Fisher, and Hakim in 1965?

The answer is no. In 1936, Riddoch published a paper called, "Progressive dementia without headaches or changes in the optic discs due to tumors of the third ventricle" (*Brain.* 1936;59:225-233). In 1956, Foltz and Ward published a paper called "Communicating hydrocephalus from subarachnoid bleeding" (*J Neurosurg.* 1956;13:546-566) and McHugh also published a paper called "Occult hydrocephalus" (*Q J Med.* 1964;33:297-312). Both these latter papers were published in or adjacent to my department in Seattle. Nevertheless, the definitive characterization which brought the syndrome to clinical attention was the report of Adams et al in 1965, and they were the first to show the efficacy of shunting.

2. Is CSF pressure really normal in patients with NPH?

The actual readings of CSF are often moderately and physiologically high because of anxious muscle tension in the patient. Then, with the needle remaining in place, the patient relaxes and CSF fluid pressure drops 15-20 mm of CSF with the patient supine and the manometer erect. It can be argued, however, that a single CSF measurement by lumbar puncture may not adequately reflect the true intracranial pressure, or the presence of numerous B waves.

3. Is NPH really a cause of curable dementia?

Bret wisely says "no" to this question. He states bluntly, "patients with NPH do not fit the criteria of degenerative (Alzheimer-type) or arteriosclerotic dementia." This is largely a semantic argument. Most neurologists accept the premise that NPH is a cause of curable dementia, particularly if strict criteria are used in establishing the diagnosis. As pointed out by Bret and colleagues this criteria includes:

- Presence of a clearly identified etiology;
- Predominant gait difficulties with mild or absent cognitive impairment;
- Substantial improvement after CSF withdrawal (CSF tap test);
- Normal sized or occluded sylvian fissures and cortical sulci on CT or MRI;
- Absent or moderate white matter lesions on MRI.

4. Is NPH specific to the adult and elderly population?

This section deals with pediatric cranial malformations, which may produce a syndrome in children analogous to that of NPH in adults with subtle mental deterioration, gait abnormalities, and delayed bladder control.

5. Is CSF diversion the only treatment modality?

Ventriculoperitoneal shunts have become standard

treatments although ventriculoatrial shunts are still a second-line treatment. Lumboperitoneal shunts have never gained widespread acceptance in the treatment of patients with NPH, probably because they are strictly limited to communicating forms of hydrocephalus. Whatever the type of shunt, the major nuisance is the high rate of complications. Thus far, only truly satisfactory ventricular drainage is effective. Third ventriculostomy in patients with aqueductal stenosis may be effective but only a few patients and their surgeons have experience with this technique.

Conclusion

Bret concludes his commentary with a number of points.

A. Some carefully selected patients respond to shunting which remains the standard today. Nevertheless, complications are high, although newer programmable shunts eliminate some of the difficulties.

B. Presently, the term "normal pressure hydrocephalus NPH" is an oxymoron, indicating a static illness. The problem lies that in reality NPH is likely to be a dynamic process that gradually and insidiously disrupts the intracranial structures.

C. It has become obvious that the other elements of the historical concept of NPH need to be revised. NPH should not be regarded as an age-related disease specific to the adult and elderly population. A similar condition may be encountered during childhood, with a clinical presentation that does not differ basically from that of the adult and may be erroneously ascribed to "arrested hydrocephalus," which is a distinct condition. More important, the term NPH is questionable because it matches neither the real conditions nor the current diagnosis. This is established in most institutions on the basis of the clinical and CT presentation only, without assessment of the ICP nor the actual CSF manometric profile of such patients. This is acknowledged by the results of dynamic tests that showed a general trend to increased, albeit compensated, pressure levels or at least an inability of compensatory mechanisms to dampen a sudden increase of ICP in patients with NPH.

Bret proposes a more relevant nosographic designation for the NPH syndrome by renaming it "chronic hydrocephalus" without reference to age and CSF pressure. Although this proposal is attractive, it is unlikely to be adopted after many decades of neurologists being taught that NPH is one of the rare treatable causes of dementia. NPH is an active process that results from failure of the resorptive mechanisms of the CSF. It may be regarded as an intermediate state of balance between uncompensated hypertensive hydrocephalus and asymptomatic hydrocephalus (in which compensatory systems are fully effective). As proved by follow-up monitoring of shunted patients, insertion of a shunt in those suffering from chronic hydrocephalus often provides a clinical cure without changes in their ventricular size. Shunting may, therefore, be regarded as an additional compensatory system allowing chronic hydrocephalus in turn to become asymptomatic hydrocephalus, which may be the only condition that really deserves the label NPH. What is truly needed to revolutionize the treatment of NPH is improved means of identifying patients who will respond to shunts. The initial results at New York Presbyterian Hospital—Weill Cornell Medical College suggest that this may be possible using sophisticated new MRI imaging techniques. **—FRED PLUM**

Ischemic White Matter Disease may Predispose to Intracerebral Hemorrhage

ABSTRACT & COMMENTARY

Source: Smith EE, et al. Leukoaraiosis is associated with warfarin-related hemorrhage following ischemic stroke. *Neurology.* 2002;59:193-197.

Ischemic white matter disease, also referred to as leukoaraiosis, is found commonly and often incidentally on CT and MRI scans. While leukoaraiosis may have significant overlap with important clinical syndromes such as multi-infarct dementia and symptomatic lacunar-type stroke, it may just as often be completely asymptomatic. These data from Smith and colleagues indicate that leukoaraiosis may be a predictor of an additional and very important clinical phenomenon; it may contribute to the occurrence of intracerebral hemorrhage (ICH) among patients anticoagulated with warfarin.

Smith et al studied 26 cases of ICH and a history of prior symptomatic ischemic stroke and compared them to patients who had a prior stroke but no ICH. All patients were maintained on warfarin anticoagulation. Both the presence and severity of leukoaraiosis on CT scanning correlated with the likelihood of ICH. Leukoaraiosis was seen in 24 of 26 ICH cases (92%) compared with 27 of 56 controls (48%), a highly statistically significant result with an odds ratio (OR) of 13. Severe leukoaraiosis conferred an OR of 25. These relationships were independent of other predictors of ICH that included a history of multiple previous strokes, an

INR of > 3.0, and the presence of carotid stenosis.

Leukoaraiosis increased the risk of ICH in both superficial and deep locations. This indicates a possible interaction between leukoaraiosis and a variety of vascular pathologies such as cerebral amyloid angiopathy (producing lobar bleeds) and hypertensive fibrinoid necrosis (producing basal ganglia hemorrhage). ICH did not generally occur at the site of the previous stroke, indicating that prior infarction was not the cause of bleeding. Rather it was more likely chronic diffuse ischemia (of which leukoaraiosis is the radiographic marker) that led to the hemorrhages.

COMMENTARY

These data raise the question of whether leukoaraiosis should be taken into account when deciding to anticoagulate patients at risk for stroke. This applies in particular to elderly patients with atrial fibrillation. As Smith et al point out, leukoaraiosis may simultaneously mark the patient who, on one hand, has a high ischemic stroke risk, but at the same time is at an increased risk for a complicating hemorrhage. Among patients without a prior stroke, and, thus, at lower risk for ischemic than hemorrhagic disease, it is possible that the presence of severe leukoaraiosis should preclude warfarin use. These data further hold implications not only for warfarin therapy, but also for the even more common use of antiplatelet drugs. While patients with leukoaraiosis are generally considered to have small vessel ischemic disease mandating agents such as aspirin, this likely narrow and largely theoretical therapeutic benefit may be counteracted by a significant risk of hemorrhage. Finally, leukoaraiosis as defined by CT may not be directly equated with MRI findings such as diffuse hyperintensities on fluid-attenuated (FLAIR) sequences. Further work using MRI data rather than CT may help to better understand this process. **—ALAN Z. SEGAL**

CME Questions

6. Statin use has been associated with a decreased risk of AD:
a. in prospective preventative trials.
b. presumptively, based on retrospective evidence only.
c. to a degree that warrants routine clinical use at this time.
d. in studies of dementia incidence but not prevalence.

7. In acute stroke patients with PWI > DWI mismatch on MRI, hyperglycemia is associated with all of the following *except*:
a. reduced penumbral salvage.
b. greater final infarct size.
c. worse functional outcome.
d. focal seizures.

8. Celiac disease is definitely associated with:
a. carpal tunnel syndrome.
b. epilepsy.
c. polyneuropathy.
d. dementia.

9. All of the following raise the risk of intracerebral hemorrhage *except*:
a. leukoaraiosis on CT scan.
b. warfarin therapy.
c. chronic hypertension.
d. remote ischemic stroke.

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As always, we are eager to hear from our readers about topics they would like to see covered in future issues. Readers who have ideas or proposals for future single-topic monographs can contact Managing Editor Robin Mason at (404) 262-5517 or (800) 688-2421 or by e-mail at robin.mason@ahcpub.com. ■

PHARMACOLOGY WATCH

WHI Trial Arm Stopped Due to Increase in Breast Cancer

Overall health risks exceeded benefits from use of combined estrogen plus progestin for an average 5.2-year follow-up among healthy postmenopausal US women" is the stunning conclusion from the Women's Health Initiative published in the July 17 *Journal of the American Medical Association*. The trial, which randomized 16,608 healthy postmenopausal women to conjugated equine estrogen/medroxy-progesterone or placebo, was stopped just 5.2 years into the 8.5 year study when the risk for invasive breast cancer exceeded the stopping boundary. Excess coronary heart disease (CHD), stroke, and pulmonary embolism (PE) were also noted; however, the combination reduced the risk of colorectal cancer, endometrial cancer, and hip fracture. The findings were front-page news coast-to-coast as well as the subject of cover stories in *Time* and *Newsweek*. Important aspects of the study include:

Although there is a higher risk of adverse events with the combination of conjugated estrogen and medroxyprogesterone, the absolute risk is low. The hazard ratios were: CHD 1.29, breast cancer 1.26, stroke 1.41, PE 2.13, colorectal cancer 0.63, endometrial cancer 0.83, hip fracture 0.66, and death due to other causes 0.92. Per 10,000 person-years, estrogen/progestin resulted in 7 more CHD events, 8 more strokes, 8 more PEs, and 8 more invasive breast cancers, but 6 fewer colorectal cancers and 5 fewer hip fractures. All-cause mortality was no different between the 2 groups.

This study, which enrolled healthy women with an intact uterus, was designed as a primary prevention trial of CHD. When combined with the results from HERS II published just one week earlier (*JAMA*. 2002;288:49-57) (a secondary prevention trial in women with known CHD), the notion of estrogen/progestin being cardioprotective is essentially eliminated.

Another wing of WHI is looking at nearly 11,000 women who have had hysterectomies and are on estrogen alone. So far, that study has not shown an increase in the rate of breast cancer, and the study will continue. The WHI group also admits that other estrogen/progestin combinations may result in different outcomes.

What to do with women on HRT who are doing well? The authors and editorialists of WHI suggest that there is no urgency, but that all women should be moved away from HRT as a strategy for preserving health and preventing disease. New patients should look for alternatives, and women currently on HRT should reevaluate the reason the drugs are being used and consider other options (*JAMA*. 2002;288:321-333; *JAMA*. 2002;288:366-367).

Side Effects Overrated in Beta Blockers

The side effects of beta blockers may be overrated by most physicians according to a new study. This leads to underuse of these important drugs, especially in cardiac patients. The authors performed a quantitative review of 15 trials, which included more than 35,000 patients. Beta

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blockers were not associated with an increased risk of depression, and only a small risk of fatigue (18/1000 patients 95% CI, 5-30) or sexual dysfunction (5/1000 95% CI, 2-8). There was no difference in these side effects with the lipid solubility of the various drugs; however, late-generation beta blockers were associated with less fatigue than the older drugs (*JAMA*. 2002;288[3]:351-357).

Aranesp Approved in Cancer Treatment

Aranesp (darbepoetin alpha), Amgen's long-acting erythropoietin, has been approved for use in cancer patients undergoing chemotherapy. The drug was initially approved for treatment of anemia associated with renal failure and dialysis. Aranesp maintains blood levels about 3 times longer than previous available erythropoietin (Procrit), allowing for dosing every 2-3 weeks as compared to weekly dosing for Procrit.

Zelnorm to Provide IBS Relief

The FDA has approved tegaserod maleate (Zelnorm—Novartis) for the treatment of women with irritable bowel syndrome (IBS) whose primary symptom is constipation. The drug is a serotonin-4 receptor agonist that is been shown to reduce constipation, bloating, and abdominal discomfort.

The approval was based on results of 3 randomized, double-blind, placebo-controlled trials each lasting 12 weeks. The efficacy of tegaserod was greater at 1 month than at 3 months, suggesting a decrease in efficacy over time. The drug is approved for short-term treatment, as long-term efficacy as well as safety is not established. The efficacy in men with constipation-predominant IBS has also not been established. Not surprisingly, the primary side effects of tegaserod are diarrhea. The approval has already come under criticism by the consumer watchdog group Public Citizen calling the approval "reckless." The group contends that users of tegaserod were more likely to need surgery in clinical trials and were also more likely to develop ovarian cysts. Public Citizen has also been critical of the FDA for reapproving alosetron (Lotronex) for the treatment of women with diarrhea predominant IBS.

FluMist Delayed for Second Time

The FDA approval of FluMist has been delayed for a second time. The intranasal, live attenuated influenza vaccine was first delayed 1 year ago when the agency requested more safety data. The current delay is due to the FDA's need for additional information regarding the manufacturer's biologics license application. FluMist may someday provide an alternative to injection based flu vaccines.

Elderly Patients: Keep Taking Your Statins!

Elderly patients frequently discontinue statin therapy on their own according to 2 new studies in *JAMA*. A large group of elderly patients enrolled in a New Jersey Medicaid and pharmaceutical assistance program were followed to assess their compliance with statin therapy over time. Based on the quantity of drugs dispensed, only 60% of patients were adhering to therapy at 3 months and only 32% at 120 months. Factors predicting poorer adherence with therapy included nonwhite race, low income, older age, less cardiovascular morbidity at the start of therapy, depression, dementia, and coronary events after starting treatment. Patients who started therapy more recently were more likely to continue therapy compared with those who started the statin therapy in 1990. In the second study, researchers in Canada looked at patients age 66 and older who were on statin therapy and fell into 1 of 3 groups: those with recent acute coronary syndrome, those with chronic coronary artery disease, and those without coronary disease who were taking statins for primary prevention. Patients older than the age of 66 had 2-year adherence rates of 40.1% for patients with recent acute coronary syndromes, 36.1% among patients with chronic CAD, and only 25.4% among those taking statins for primary prevention. As pointed out in an accompanying editorial, both studies are based on pharmacy databases, which are only a surrogate for compliance; however, the sheer size of the studies and the magnitude and consistency of the trends noted make the findings likely be correct. In light of the recent National Cholesterol Education Program recommendations, which dramatically increases the number of elderly patients eligible for statin therapy, compliance programs in this population are needed (*JAMA*. 2002;288:455-461; 462-467; 495-497). ■

NEUROLOGY ALERT®

A monthly survey of developments in neurologic medicine

CUMULATIVE INDEX

Volume 20, Numbers 1-12, Pages 1-96

September 2001—August 2002

A

alcohol, dementia, 7:51
alcoholic polyneuropathy, 1:8
Alzheimer's disease
  beta amyloid, 3:17
  cholesterol, 4:29
  homocysteine, 11:85
  microglia, 2:9
  soluble amyloid protein, 11:81
  vaccine, 8:64
American Academy of Neurology meeting, 10:73
amyotrophic lateral sclerosis, 10:80
antiepileptic drugs, 10:79
antiherpes virus therapy, 7:56
anti-hu polyneuropathies, 7:54
ataxia, genetics, 5:37

B

back pain, chiropractic treatment, 12:94
bell's palsy, prognosis, 11:87
beta amyloid, Alzheimer's disease, 3:17
beta-oxidation disorders, 12:92
brachial plexus injury, neonates, 9:65
brain atrophy, dementia, 5:38

C

caffeine, Parkinson's disease, 1:4
CANOMAD, 4:31
cardiac arrest, 10:75
carpal tunnel syndrome, 7:53
children
  head injury, 3:19
  language regression, 1:6
  vaccinations, 2:15
chiropractic treatment, back pain, 12:94
cholesterol, Alzheimer's disease, 4:29
chronic inflammatory demyelinating polyradiculoneuropathy
  IVIG, 4:31
  PO protein, 4:31
colchicine myopathy, 7:55
complex regional pain syndrome, 8:63
computed tomography, meningitis, 6:41
connective tissue disorders, 9:68
coronary artery bypass, stroke, 1:4
cyclophosphamide, myasthenia gravis, 12:90

D

dementia
  alcohol, 7:51
  brain atrophy, 5:38
  vascular, 10:76
depression, vagal nerve stimulation, 8:64
dopamine, stroke, 3:22
drug resistance, epilepsy, 9:71
drugs, antiepileptic, 10:79
dystonia
  focal hand, 12:92
  focal task-specific, 2:12
  primary, 9:70

E

electrical stimulation, nerve injury, 9:67
encephalitis, 8:59
encephalomyeloradiculitis, 11:82
endarterectomy, elderly, 1:5
epilepsy
  antiepileptic drugs, 10:79
  drug resistance, 9:71
  sudden unexplained death, 11:88
  temporal lobe, 1:1
Epstein-barr virus, multiple sclerosis, 6:45
essential tremor, 6:42
eye strain headache, 11:86

F

familial periodic paralysis, 11:83
fatigue, multiple sclerosis, 9:66
focal hand dystonia, 12:92
focal task-specific dystonia, 2:12

G

gamma knife surgery, 6:44
genetics
  ataxia, 5:37
  movement disorders, 3:18
  primary dystonias, 9:70
Guillain-barré syndrome, 6:47

H

head injury, children, 3:19
headache
  eye strain, 11:86
  paroxysmal, 8:57
  tension, 7:54
hemicrania continua, 8:57
heparin, stroke, 5:34
high-grade glioma, 10:77
homocysteine, Alzheimer's disease, 11:85
HRT, stroke, 5:36
Huntington's disease
  pathogenesis, 4:25
  treatment, 4:25
  variant, 6:43
hypertension, intracranial, 7:49

I

interferon-beta, 1:7, 10:78
intracranial hypertension, 7:49
ischemic forearm test, 2:15

L

language regression, children, 1:6
Lewy bodies, 8:60

M

meningitis, computed tomography, 6:41
microsurgery, spinal stenosis, 9:69
migraines
  American Migraine Study II, 3:20
  genetics, 1:3
  menstrual, 11:87
  oral triptans, 5:39
mild cognitive impairment, 2:13
modafinil, 9:66
movement disorders, genetics, 3:18
multiple sclerosis
  antiherpes virus therapy, 7:56
  epstein-barr virus, 6:45
  fatigue, 9:66
  interferon, 1:7, 10:78
  modafinil, 9:66
  prevalence, 7:55
  steroids, 4:30
  treatment, 9:72
muscle radiography, 6:46
myasthenia gravis
  antibodies, 8:62
  cyclophosphamide, 12:90
  ocular, 3:21
  tacrolimus, 6:48

N

neonates, brachial plexus injury, 9:65
nerve injury, electrical stimulation, 9:67
nerve stimulation, 3:23
neuroethics, 12:94

O

ocular myasthenia gravis, 3:21

P

paralysis, familial periodic, 11:83
Park6-linked parkinsonism, 7:52
Parkinson's disease
  American Academy of Neurology meeting, 10:73
  caffeine, 1:4
  gamma knife surgery, 6:44
  intensive voice treatment, 4:30
  Lewy bodies, 8:60
  pathogenesis, 4:26
  smoking, 6:44
  subthalamic stimulation, 11:86
  treatment, 4:26
paroxysmal headache, 8:57
patent foramen ovale, 7:52
pathological laughter and crying, 4:28
primary dystonias, genetics, 9:70
primary lateral sclerosis, 4:27

R

repetitive nerve stimulation, 3:23

S

schizophrenia, adolescence, 5:33
single fiber EMG, 3:23
sixth nerve palsy, 3:24
Sjogren's syndrome, 2:16
sleep apnea syndrome, 8:61
sleep drugs, 8:64
smoking, PD, 6:44
soluble amyloid protein, 11:81
spatial awareness, 2:11
spinal stenosis, 9:69
spinal tap, 5:38
status epilepticus, 8:60
steroids, multiple sclerosis, 4:30
stiff-person syndrome, 6:46
stroke
  chronic infection, 12:91
  coronary artery bypass, 1:4
  dopamine, 3:22
  folate, 11:85
  heparin, 5:34
  homocysteine, 11:85
  HRT, 5:36
  inosine, 12:89
subthalamic stimulation, 11:86
sudden unexplained death in epilepsy, 11:88
syncope, 2:10

T

tacrolimus, 6:48
temporal lobe epilepsy, 1:1
tension headache, 7:54
Tourette syndrome, 2:14
tremor, 6:42

V

vaccines
  Alzheimer's disease, 8:64
  children, 2:15
vagal nerve stimulation, depression, 8:64
vascular dementia, 10:76
viral encephalitis, 8:59
voice treatment, Parkinson's disease, 4:30