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Staining for Apoptosis: Now Neuropathologists Can "See" Leukoaraiosis

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Implications of a Reliable Method for Quantifying Brain Injury Associated with Repair of Carotid Artery Stenosis

Surgical intervention involving the left-sided circulation anatomically or functionally proximal to the head is capable of inducing emboli to the brain. Müller et al (page 47) in this issue of the *AJNR* convincingly show new diffusion-weighted imaging lesions associated with carotid endarterectomy (CEA) in 26 of 77 surgeries. Most of these lesions represent infarcts arising from emboli, and most of these infarcts were clinically silent. The incidence of clinically evident perioperative neurologic morbidity for CEA in Müller's series (6%) is similar to that found in the NASCET trial (<7%). I agree with the authors that the incidence of new lesions detected with diffusion-weighted imaging is astonishingly high, but it is predictable. Anyone who has done transcranial Doppler sonography during CEA or cardiac surgery supported by cardiopulmonary bypass (CPB) knows that many emboli can be detected during these procedures. Characterizing the emboli, whether air or particulate, cannot be achieved by means of the sonographic device.

I believe that microembolic signals on Doppler sonograms are important. Müller and colleagues have confirmed in CEA patients what Stump et al (1) observed in CPB patients: greater numbers of detected emboli are associated with poorer outcomes (greater decrement on prospective neurobehavioral testing in Stump's series). Reducing the number of cerebral infarcts associated with CEA is a laudable objective, even if most of them are clinically silent.

In a previous editorial (2), I suggested there was a role for neuroradiologists in making cardiac surgery safer. Investigations have shown that standard T1- and T2-weighted MR images are not sufficiently sensitive for detecting many subtle lesions associated with CPB (2). I hoped that diffusion-weighted imaging, perfusion imaging, or both would be sufficiently sensitive to achieve this (2). Müller and colleagues have made an important contribution to the literature, and their findings need confirmation by researchers at other centers. In future investigations, MR imaging should be performed after diagnostic arteriography and before surgery, followed by MR imaging 1 to 2 days after surgery.

These findings suggest an opportunity for two further lines of investigation. The first is the testing of various neuroprotective interventions, the end point being determination of the number and vol-

ume of new lesions revealed by diffusion-weighted imaging. CEA patients are ideal for this type of study, more so than CPB patients, because the research subject has a large brain, the time of the insult is known, and the subject is not too sick for repeat imaging 24 hours after the insult. Approximately half of CPB patients have a temporary pacemaker, and CPB patients are often uncooperative for several days after surgery. If we anticipate that the tested pharmaceutical agent would reduce the incidence of lesions by 50%, and without intervention we expect a 33% incidence of detectable lesions, then a study group composed of 212 patients would give 80% power for rejecting the null hypothesis (that the intervention has no benefit). Therefore, the sensitivity of diffusion-weighted imaging is sufficient to derive meaningful information from a relatively small study sample.

A second, additional line of investigation relates to the considerable current interest in alternative approaches for the treatment of symptomatic and asymptomatic carotid stenosis. Cardiologists and interventional radiologists in some centers routinely employ endovascular stenting. Proponents of these innovative approaches should be encouraged to go head-to-head with surgeons employing the more conventional open-neck, open-vessel surgery in order to determine the safer treatment.

Neuroradiologists are well positioned to assume a pivotal role in such studies. My hope is that members of our profession can find the time and energy to assemble an appropriate team of collaborators and take a leadership position in these important activities.

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Staining for Apoptosis: Now Neuropathologists Can "See" Leukoaraiosis

On a case-by-case basis, neuropathologists can have a challenging time explaining the abnormal T2 white matter hyperintensity referred to as leukoaraiosis. In some cases, such as that described by Brown et al (page 79), there is a very satisfying correlation between the MR-revealed lesion and a discrete, focal loss of myelinated fibers without the complete destruction of tissue that one sees in lacunar infarct. It is not uncommon, however, to see only some scattered reactive astrocytes, slightly faint myelin staining, or even nothing at all. Such an ephemeral lesion is disquieting to a pathologist who is less accustomed than a radiologist is to dealing with the "shadowy." Brown et al have now identified a candidate underlying molecular process that has the potential to explain this range of microscopic morphologies. That process is apoptosis.

The literature contains about 30,000 reports on the mechanism, cause, and role of apoptosis in various processes. Twenty-five thousand of these have been published in the past 2 years. One almost expects this epidemic to appear on the cover of a weekly news magazine. Whatever the Greek roots of the term "apoptosis" originally meant, it is now best understood to mean a regulated cell death. It is an organism's way of actively eliminating a cell that is no longer functioning properly or that has a high likelihood of malfunctioning in the future. Apoptosis is an important part of normal cellular turnover in a variety of tissues. It is involved in removing cells irreversibly damaged in progressive degenerative diseases. A critical part of the survival strategy of cancer cells is to acquire mutations that inactivate the molecular machinery mediating this process. Programmed cell death is a developmental process in which excess precursor cells are pruned back apoptotically in the generation of normal tissue structures. Therefore, investigators in a wide range of disciplines have had to become familiar with this process, including neuroradiologists.

Conceptually there are three components to apoptotic cell death: 1) generating and sensing a signal that continued cell survival is no longer advantageous, 2) transducing this signal throughout the cell by activating a cascade of proteases (caspases) that activate downstream caspases and cleave various cellular, structural, and regulatory proteins, and 3) terminating the viability of the cell by cleaving the genomic DNA into small fragments. The purpose of this highly regulated process, disassembling the cell from the inside out, is to remove the cell in such away that there is no residual debris to incite inflammatory processes and scarring. There are many types of initiating signals, and important differences in the caspase cascade in different cell types, but the final effect is

always systematic DNA cleavage. Therefore, documentation of this endpoint is the most comprehensive method of identifying apoptotic cell death. When the DNA is systematically cleaved, a large number of fragment ends are exposed; these can be labeled using a biochemical technique usually referred to as TUNEL staining. Although there are important biologic and technical caveats, a cell with a TUNEL-positive nucleus is a cell that is undergoing apoptosis.

The central observation of the Brown et al case report is that within a defined region of leukoaraiosis there are more oligodendroglia undergoing apoptosis than in adjacent areas. At first, the numbers may seem unimpressive; there are only twice as many TUNEL-positive nuclei within the defined region compared with control areas. Nonetheless, because the number of oligodendroglia within the area of leukoaraiosis is greatly depleted, the percentage of cells caught in the act of apoptosis is actually quite high. The presence of TUNEL-positive cells within control areas and in the vascular endothelium is a testament to the normal rate of physiologic cell turnover in these areas. Significantly more work is necessary to determine to what extent this rate can be increased before the replicative capacity of replacement cells is exceeded and net cell loss occurs.

The study of Brown et al goes a long way in explaining the troubling apparent lack of correlation between radiographic leukoaraiosis and pathologically observable morphologic lesions. Without the labeling of the TUNEL stain, it is very hard to see apoptosis. The nuclear morphologic changes observable by standard histologic stains are subtle, and may only persist for a matter of hours. It is likely that the TUNEL staining approach will document areas of increased oligodendroglial dropout in zones of leukoaraiosis that have previously appeared fairly normal by conventional histologic analysis. The ability to see these "early" zones of leukoaraiosis will open the door to a greater understanding of this pathophysiologic process. For example, is vascular collagenosis present in these early lesions, implying causality? Or are these changes merely part of the end-stage disease?

The biochemical and cellular meaning of MR hyperintensity is very complex. Clearly a region of decreased myelin and increased free water (extracellularly in the perivascular space as well as within astrocytic cytoplasm) such as exists in this case report should have increased signal on T2-weighted images. A more complex question is, how much molecular disorder is there in a degenerating apoptotic oligodendroglial cell or immature regenerative myelin created in the repair process? The devel-

opment of this potential morphologic marker for foci of leukoaraiosis will certainly make neuropathologists more interested in these lesions. More extensive radiologic analyses such as diffusion-weighted MR imaging may subdivide foci of leukoaraiosis into different lesions, which can then be distinguished morphologically.

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The Residents Did Not Miss Many? Are You Kidding?

It is noteworthy that the *AJNR* has published a study assessing the consequences of misinterpretations of neuroradiology CTs by on-call radiology residents. If the results had shown significant misses, such an article could become fodder for plaintiff attorneys seeking settlements from teaching hospitals in medical malpractice cases alleging misdiagnosis of neuroradiologic studies such as CTs and MR images of the brain and spine. I can hear the cross-examination now: "Isn't it true, doctor, that the authoritative journal, the *AJNR*, published an article stating that residents routinely misinterpret neurodiagnostic imaging studies on call? Isn't it malpractice to have these studies read by residents without supervision, doctor?"

This would indeed be a frightening situation; fortunately, the accusation is not true. In this issue, Lal et al (page 124) testify that on-call residents do very well in the specific and focused task of interpreting emergency neuroimaging studies. The images evaluated in this study were mostly CT scans of the brain obtained emergently because of acute neurologic problems, and these are arguably among the most important studies regarding subsequent clinical management. The on-call radiology residents in this study had an enviably low miss rate (0.9%) of significant findings on CT, and it was even rarer for patient outcome to have been negatively affected (0.08%). These figures are heartening.

One interesting fact peculiar to this study, and probably not amplifiable to generalizations, was the lower rate of misses by junior as opposed to senior residents, with three being the greatest number of errors made by a resident. Thirty-three of the misses did not influence patient treatment or outcome; only two misses had a potentially serious effect. In one case, an atypical pattern of basal ganglia calcification was misinterpreted as possible hemorrhage. As a result, the patient did not receive thrombolysis for an early stroke, the clinical results of which tend to be uncertain. The other error involved missing a cerebellar stroke, which can be difficult to diagnose because the posterior fossa beam-hardening artifacts on CT are notorious for interfering with diagnostic accuracy. Overall, this is a good track record.

Of course, those charged with teaching residents suspected this would be the case. Residents, by the

time they take emergency call, have been exposed to enough didactic and other teaching material to identify abnormalities. Residents tend to be overly cautious and probably notice minutiae that an attending might not, even though the minutiae may be of no clinical significance. I never have had a problem with a house officer noticing too much on an examination; it is a problem when findings are missed. We want the residents to see and document everything, even at the expense of a long dictation.

There are a few residents I have known over the years who, fortunately for the authors, were not involved in this study. Residents learn at different rates, require different handling, and are capable of accepting different degrees of responsibility after the same number of years of training. There are one or two who resist training of any sort. Some believe they already know enough, some are not receptive to training, and some are not motivated to learn.

The number of problem trainees is low because, in general, we are able to select motivated house officers. Even an excellent resident cannot be expected to make the correct radiographic interpretation 100% of the time—a fact the law recognizes. Even in malpractice suits, the law only requires that a physician be reasonably prudent and apply the "standard of care" to every case in which they are involved. The law does not mandate that the physician be 100% correct 100% of the time, but that the physician must do his or her best. This is what we strive to do and what we train the residents to emulate, knowing full well that 100% accuracy is not attainable.

Nevertheless, it behooves us to be aware of individuals in the population who feel that residents-in-training might represent a risk to patients. One particularly vocal and extremely well-organized group headquartered in the Tampa Bay area is the Association for Responsible Medicine. I recommend visiting this organization's web pages at <http://www.a-r-m.org/tortquest.htm> and <http://www.a-r-m.org/armact.htm> to see how one cadre of patients views the quality of care rendered by residents in teaching institutions. At the second web site, be sure to read the first case history listed at the bottom of the page, titled "Teaching Malpractice."

Mistakes do happen in medical care, and misinterpretations, though infrequent, are at some level unavoidable. Are residents more likely to make mistakes than attending physicians, or for that matter, private practice physicians? I do not think it is inevitably so. This article supports that view and

allows us to continue to train residents and fellows appropriately.

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Guidelines for Diagnostic Neuroangiography: A Model to Emulate from a Neuroradiologist's Perspective

The *Quality Improvement Guidelines for Adult Diagnostic Neuroangiography* published in this issue (page 146) is an extremely important document for three reasons. First, it is the result of the joint efforts of the three radiologic subspecialties whose members perform the overwhelming majority of these procedures. Second, the criteria focus on quality of procedural performance by any physician undertaking the procedure, rather than credentials based upon training. Third, the standards are based upon data derived from the literature and evaluated by a group of experts in procedural performance to reach a consensus. Each of these points is significant and deserves further explanation.

Members of the three societies who have authored this document perform the most neuroangiography, so the experience and expertise needed to review and evaluate the literature is represented. The members of the American Society of Neuroradiology (ASNR) and the American Society of Interventional and Therapeutic Neuroradiology (AS-ITN) deal with problems of the brain and the spinal cord, and the blood supply to these organs, on a daily basis. Using a variety of procedures, including neuroangiography, their professional careers are devoted to imaging these organs. The members of the Society of Cardiovascular and Interventional Radiology (SCVIR) also perform catheter-based procedures on a daily basis, including a large number of neuroangiographic studies, especially in the nonacademic world. Members of the SCVIR have had extensive experience developing practice standards and guidelines, and have pioneered the quality improvement (QI) approach in radiology. Rather than one society producing a parochial standard by excluding the input and experience of the others, these three societies have joined forces to produce a document that has one goal: the assurance that this procedure is performed at the highest level possible, for the benefit of patients.

The training of the radiologist to perform neuroangiography properly is highly variable, whether or not the individual is a member of one of the three mentioned societies. In addition, members of a number of nonradiologic specialists currently perform, or would like to perform, neuroangiography (possibly to accompany more complex therapeutic procedures), including cardiologists, vascular surgeons, neurologists, and neurosurgeons. Each group feels its members have a "right" to perform

neuroangiography, based upon often poorly documented "training". Some have even composed self-serving documents to substantiate this "right". The QI approach changes the "game" from one of "training" and credentialing to one of actual performance.

Most institutional credentialing committees will surely require some documentation that a practitioner has been trained to perform neuroangiography. As the procedures are performed, however, data will be collected. Each practitioner must adhere to specified thresholds of indications, success rates, and complication rates. If these thresholds are exceeded, a review will be initiated. Improvement is the goal, but loss of privileges is the risk. A practitioner no longer will be able, whatever the specialty, to advocate his/her "right" to perform neuroangiography. The practitioner will be forced to quote his/her own complication rates to a patient, instead of those from the literature, so that the patient may make a meaningful decision regarding risk and benefit. Institutional credentialing committees will not be faced with debilitating "turf wars"; the numbers will speak for themselves.

We hope this methodology will become a model for other procedures and interventions, both within and outside of radiology. The Joint Commission on the Accreditation of Health Care Organization (JCAHO) has already established that the QI methodology will become the "measuring stick" of the future. Therefore, it is incumbent upon us to become familiar with the techniques and to begin producing our documentation. This methodology will also protect our specialties from those who would attempt to undertake procedures that we practice so diligently. We should not be afraid of displaying and documenting our expertise; it is to our ultimate benefit.

What about the methodology used and the numbers advocated as thresholds? The authors have used a modified Delphi approach, requiring them to review the literature in order for experts to reach a consensus on reasonable standards. This is not pure science; it is not a meta-analysis only. It is based upon experts examining the literature, evaluating its quality, and reaching an agreement. The thresholds for indications and success rates are straightforward and need no explanation. The definitions for complications and their thresholds, however, require discussion.

The non-neurologic major complication rates are rather generous, in my opinion. The amount of contrast medium used for the average cerebral angiogram is below that used for an enhanced CT of the brain. Most angiographers use a nonionic agent, so renal failure is probably very rare after neuroangiography. Arterial injuries requiring intervention, or persistent bleeding requiring transfusion, are exceedingly rare in my experience.

The neurologic complication rates require the most scrutiny. Some may consider the definition for a transient ischemic attack (TIA) rather broad. Imaging studies, such as diffusion MR imaging, have changed our concepts of TIAs and small strokes as well as of reversibility and irreversibility of injury to tissue. A TIA is probably a rather short event, lasting minutes to a few hours. Nonetheless, the authors have grouped TIAs and reversible strokes together, so the issue of definition is moot. The allowed rate of 2.5% is generous.

The most feared complication of neuroangiography is a permanent neurologic deficit. A rather wide range is cited from the literature, and the authors have wisely chosen a value on the lower end of this range. This is the complication that must be the most closely evaluated, because the consequences are the greatest. A rate of 1% is generous; a good practitioner of this admittedly complicated procedure should never exceed such a number. How "generous" is this rate? A recent article by Cloft et al (1) describes a meta-analysis of three recent prospective studies of complications among patients with subarachnoid hemorrhage, cerebral aneurysm, and arteriovenous malformation who underwent cerebral angiography.

There was a permanent neurologic complication rate of 0.07%. This series did not include patients undergoing angiography for cerebrovascular occlusive disease, which is the group, in my experience, with the highest neurologic complication rate. The low rate of permanent neurologic complications, however, supports the generosity of the rate in this QI document, a rate that any experienced angiographer should meet easily. It should be emphasized that the authors list thresholds only as guides for an institution. Case mix and other factors may require specific QI rates to be altered.

In summary, the authors are to be congratulated for presenting a number of models to us. Neuroangiographers from multiple societies, in a model of cooperation, were willing to focus their efforts to produce an excellent document that has quality patient care at its heart. It is a model for the future development of guidelines for other image-guided procedures. We hope it will be a model for the rest of medicine.

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Toward an Understanding of Syringomyelia: MR Imaging of CSF Flow and Neuraxis Motion

Pathophysiologic mechanisms causing syringomyelia among patients with the Chiari I malformation have attracted considerable interest, but remain poorly understood. It is generally thought that alterations in CSF flow resulting from tonsillar obstruction at the foramen magnum lead to abnormalities in fluid pressures in the spinal canal and cord. But why do some patients with low tonsils develop syringomyelia and others do not? In this issue of the *AJNR*, Hoffman et al (page 151) attempt to elucidate the pathogenesis of Chiari-associated syringomyelia by measuring CSF flow patterns and cord pulsations. There are a number of technical limitations in this study, including the use of a low temporal sampling rate that may not accurately depict rapid changes in cord motion and CSF flow. Analysis of flow measurements was limited to comparison of maximum volumetric flow rates. CSF flow changes were observed, but were not statistically significant. Nonetheless, systolic and diastolic cord pulsations were higher among

patients compared with healthy volunteers, and among patients with syringomyelia compared with patients without syringomyelia. This selective change in a dynamic parameter appears to correlate with disease and requires further evaluation.

The embryogenetic model of syringomyelia postulates pathologic alterations in neurogenesis as the basis of the structural abnormalities that lead to syringomyelia. The hydrodynamic theorists attempt to explain the changes in syringomyelia as the result of disturbances to processes that alter fluid dynamics. Alterations of flow parameters can thereby be interpreted as phenomena resulting from the underlying structural or hydrodynamic abnormalities. Conventional MR imaging provides the necessary anatomic information on structural parameters, such as degree of tonsillar herniation, amount of obstruction at the foramen magnum, distribution and size of the syrinx, as well as the presence of other anatomic lesions or tissue relaxation changes. Flow studies provide additional information about phys-

ologic parameters, such as CSF flow patterns and motion of the neuraxis. Application of other techniques, such as diffusion imaging and spectroscopy, may eventually provide useful additional data on the intrinsic and metabolic properties of the neuraxis.

Presently, a number of studies using MR have reported changes in CSF flow, tonsillar motion, and syrinx characteristics. In certain cases, some parameters were found to vary with the degree of disease and the effects of operation. Undoubtedly these changes are related to the disease, but are measures primarily disease-specific markers or epiphenomena? The physiologic parameters that we presently observe are the effect, not the cause, of the disease—*post hoc ergo propter hoc*. Can the measurements aid in establishing a diagnosis and predicting disease formation, progression, and outcome? Unfortunately, it is presently unclear how changes in these structural and physiologic parameters are linked to the pathogenesis of syringomyelia. More specifically, the basic mechanisms involved in syringomyelia are still not well understood.

Although cord motion abnormalities may sometimes be associated with syringomyelia, they do not directly explain the pathogenesis. Caudal spinal cord motion is usually maximal at an instant of low CSF flow (near CSF end-diastole/beginning systole) and thereby does not appear directly related to systolic spinal pulse pressure abnormalities. In addition, the actual intraspinal fluid displacement caused by caudal cord displacement is very small, and should not cause significant pulse-pressure waves. Rather, the caudal motion of the cord, tonsils, and brain stem may be more significant in contributing to the resulting intraspinal (and intracerebral) pulse-pressure abnormalities through an increased obstruction at the foramen magnum. Present studies suggest that if the central canal does not communicate with the fourth ventricle (non-communicating syringomyelia), exaggerated spinal pulse pressures may lead to increased transmedullary pressure gradients and force movement of interstitial fluid across the spinal cord. Depending on the degree of patency of the central canal and the nature of the intramedullary fluid pathways, syringomyelia could also develop in communicating and parenchymal syringomyelia; signal changes and reversible enlargement of the cord may develop in the presyrinx state.

Abnormalities in cord motion have been observed in a number of diseases. The hypothesis that increased cord motion may be associated with low tonsils and syrinx development is inconsistent with a number of pathologic observations. How would syringomyelia develop in Chiari patients where

cord motion is decreased owing to tethering? Cord motion may not be increased among patients with low tonsils, with or without syringomyelia. In some cases, cord motion may actually be reduced because of scarring or significant compression at the foramen magnum. The appearance of low tonsils in intracranial hypotension can mimic Chiari and lead to misdiagnosis, but cord motion is decreased rather than increased. In fact, cord motion abnormalities in syringomyelia may not always be associated with low tonsils. Non-Chiari syringomyelia can be associated with etiologies such as arachnoiditis, soft-tissue lesions, trauma, and other structural spinal lesions in the subarachnoid space; it can also reveal abnormalities of CSF flow and neuraxis motion. The basic mechanism of syrinx development in these disorders may also involve increased CSF pulse pressures arising from obstruction of the subarachnoid space, similar to that found in Chiari-associated syringomyelia.

Although increased cord pulsations may reflect the degree of functional narrowing at the foramen magnum, they are not specific to Chiari-associated syringomyelia; they are seen in other entities with spinal canal narrowing. Surprisingly, cord motion may actually increase in cases with spinal canal stenosis, provided there is not any significant cord compression or tethering. In our experience, this phenomenon can occur in a number of different diseases involving partial restriction of cord mobility. Owing to an obligatory decrease in transverse cord mobility at the foramen magnum in Chiari, the intracranial systolic pulse pressure may be transmitted to the spinal cord primarily in a longitudinal direction, thereby increasing caudal cord motion. In addition to other pathophysiologic effects, such as altered cranial CSF ejection dynamics, the increased caudal cord impulse in Chiari may be a reflection of the decreased free space at the foramen magnum.

CSF flow abnormalities can be useful and sensitive measures for the evaluation and identification of a primary abnormality, but may originate at sites remote from the region of altered flow because of the complex nature of fluid wave propagation. In some cases, identifying the degree and location of neuraxis motion abnormalities may provide additional information to target the structural causes more accurately. Thus, observing both CSF and cord dynamics may be useful for identifying more precisely the nature of the offending pathology, especially in complex cases with multiple abnormalities.

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