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Funded Research and Neuroradiology

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A Careful Neurologic Examination Should Precede Neuroimaging Studies in HIV-Infected Patients with Headache

Headache is a common symptom in patients with HIV infection. It is the most common form of pain, more common than painful peripheral neuropathy, and has been reported as the presenting manifestation of AIDS in 12.5% to more than 55% of patients (1). Headaches in HIV-infected patients may be caused by HIV-associated aseptic meningitis, antiretroviral and other therapies, or opportunistic infections and neoplasms arising in the face of impaired cellular immunity. Causes of the latter are legion and include opportunistic infections such as CNS toxoplasmosis, cryptococcal meningitis, primary central nervous system lymphoma, and lymphomatous meningitis. Sinusitis is common with advanced HIV immunosuppression and is also a potential cause of headaches. The frequency with which significant disease is determined to be the cause of headache in this population is highly dependent on the nature of the population studied. For instance, Goldstein found serious underlying disease in 40 (82%) of 49 patients in a study of hospitalized patients (2), whereas Singer found that intracranial opportunistic infection or tumor was present in only 4% of HIV-infected patients presenting as outpatients (3). Nevertheless, the vast majority of headaches in HIV-infected patients are no different from headaches in a control HIV-uninfected population (l). These headaches bear no relation to CD4 T-lymphocyte counts, cerebrospinal fluid parameters, cranial MR imaging abnormalities, the presence of sinusitis, or the use of zidovudine (1). They have been associated with polypharmacy, depression, anxiety, and insomnia, and are often relatively unresponsive to conventional headache therapies (4). Multiple causes of headaches may be observed in a single patient.

When confronted by an HIV-infected patient complaining of headache, the treating physician's chief concern is the presence of a life-threatening, treatable illness. Does the patient have an intracranial mass lesion or meningitis? Unfortunately, no consensus has evolved regarding the best diagnostic approach for the evaluation of the HIV-infected person presenting with headache. The absence of fever, neck stiffness, and altered mental status has been suggested as effectively eliminating the possibility of meningitis, but whether this remains true in the HIV-infected population is open to question. Neurologists with experience in treating patients with AIDS recognize the importance of CD4 cell counts in their approach to management of the HIV-infected patient with headache. Generally, in the absence of significant immunosuppression, CT or MR imaging is not suggested unless focal findings are present on neurologic examination.

The findings in the study by Graham and colleagues (page 451) are not unexpected; their population was screened in advance. Allegedly, none had altered mental status, meningeal signs, neurologic findings, or ''the worst headache of their life.'' In their HIV-seropositive population without significant immunosuppression, defined as having a CD4 cell count >200 cells/cu mm, no abnormal findings on unenhanced and contrast-enhanced cranial CT scans were noted. Even in the group with CD4 cell counts <200 cells/cu mm, only 14 (15.7%) of 89 had mass lesions and another 4 (4.5%) had white matter lesions. This is not unlike observations found with CSF analysis in which CD4 cell counts >200 cells/cu mm militate against the likelihood of finding opportunistic infection. Although it is clear that the risk of opportunistic CNS infections greatly increases when CD4 cell counts drop below 200 cells/cu mm, these infections certainly occur in patients with higher cell counts. Approximately 10% of AIDS patients with cerebral toxoplasmosis or progressive multifocal leukoencephalopathy (PML) have CD4 cell counts >200 cells/cu mm.

Importantly, Graham and colleagues do not address the quality and thoroughness of the neurologic examinations performed. Surely there is a difference between the hurried house officer's examination in an emergency room and the refined examination performed by an experienced neurologist for probing the characteristics of a headache and eliciting subtle focal neurologic abnormalities. This is an essential point. How many of the 14 patients with intracranial mass lesions would have exhibited absent spontaneous venous pulsations on funduscopy, a subtle upper extremity drift, limb incoordination, increased tone, or sensory loss had a neurologist performed the examination? A careful history is equally important. A convincing history of migraine or cluster headaches, even in the face of severe immunosuppression, militates strongly against opportunistic infection or space-occupying lesions (4). Similarly, chronic daily headaches, defined as daily and near-daily headaches lasting for more than 4 hours per day for more than 15 days per month for more than 1 month, argues against underlying identifiable intracranial disease, particularly in the absence of abnormalities on neurologic examination (4). A neurologic consultation is more cost-effective than either a CT scan or an MR examination. Additionally, other neurologic complications of HIV infection, such as early cognitive impairment, peripheral neuropathy, or myelopathy, may be recognized, whereas they easily may be overlooked without careful neurologic examina-

tion. While obtaining a CD4 cell count is certainly worthwhile, as the authors suggest, for patients on antiretroviral therapies, this result is generally available from outpatient studies proximate to the time of the patient's presentation with headache. CD4 cell counts are not inexpensive nor is a test performed in an urgent fashion—facts providing another argument for a formal neurologic consultation when evaluating the HIV-infected patient with headache.

The presence of mass lesions or meningeal enhancement (not observed among the patients in this study) is the major concern. Cerebral atrophy and white matter lesions as described by the authors are not particularly relevant when addressing the issue of headaches. Although both may be features of HIV dementia, HIV dementia does not appear to be a cause of headache. The authors present insufficient data to determine whether the white matter lesions seen were the consequence of PML, which may on occasion be associated with headache. Headache in isolation, ie, without focal neurologic abnormalities, however, would be highly unusual for PML.

Graham and colleagues have demonstrated a relationship between significant immunosuppression (CD4 cell count <200 cells/cu mm) and the presence of intracranial abnormalities at the time of CT scan. They demonstrate that even in the immunosuppressed population, clinically relevant lesions remain relatively rare. Many questions remain regarding the best approach to the evaluation of these patients; however, the value of a thorough and precise neurologic examination in the evaluation of these patients cannot be underestimated.

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> Research grants . . . are the most widely-accepted measure of productivity. . . . [They] recognize past contributions as well as good ideas and plans for future work. The process of writing a fundable research proposal is a major creative undertaking and it is recognized as such by peers. Research grant dollars are a measure of research value, because the value of the product is equal to its cost of production.
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> *Karl Lanks* (1)

Funded research has value for the individual investigator, for the radiology department and the institution, for our profession, and ultimately for our patients. For some of us, having an external source of support is the only way research can be conducted. Grant funding buys the investigator time away from clinical duties. Funding provides supplies and statistical support, and it pays the rent for the imaging instrument on which the experiment is to be performed. External funding is highly valued by the administrators at an institution, and obtaining it distinguishes an investigator from other faculty. In fact, it often results in fast-track promotion and appointment to important institutional committees. Radiology committees are liberally sprinkled with individuals who believe extramural funding is an essential attribute in a candidate for department chair. It is their desire that, under the new chair, the radiology department will improve. Many believe that one cannot effectively promote research unless one has ''been there'' and knows first-hand the effort and sacrifice that must be expended to compete successfully for extramural funding. At another level, in the selection process for members of NIH initial review groups, study sections, administrators endeavor to choose individuals who are currently funded.

There is subtle, but real, disapproval by our more clinically oriented colleagues of the contributions of individuals spending more of their time on research. This resentment is perceived by trainees (2). It is crucial for a chairman to establish an environment in which the effort of investigators is recognized as important for the prestige of the department nationally and internationally. Funded research is critical for the very survival of an academic department. Individuals with the power to dismember radiology value extramural funding; it brings in considerable indirect support, which the dean can use at his/her discretion, and which can amount to 40% to 100% of the direct costs of performing the project. An accelerating number of awards enhances the reputation of the university. Consequently, this factor is germane to the equation when issues of turf are discussed. Among the three missions of a medical center—teaching, patient care, and research—only the last can be objectively quantified. The annual tabulation of research funding by federal government agencies (NIH, National Science Foundation, Departments

of Energy and Defense, etc.) is closely watched by institutional administrators. The institution's ''class rank'' is on display. In fiscal year 1998, there were 1509 active grants classified as ''imaging'' in the NIH extramural program (3). In this enterprise, radiologists play a minor role. For the 1997 fiscal year, 59 MDs or MD/PhDs in radiology departments were Principal Investigators (PIs) on NIH grants. In the 1998 fiscal year, the number rose to 87. One hundred ninety-eight of these imaging grants are sponsored by the National Institute of Neurological Diseases and Stroke (3). Many more imaging grants concerned with the central nervous system have been awarded by the National Cancer Institute (NCI) and the institutes on aging (NIA), drug abuse (NIDA), alcohol abuse (NIAAA), research resources (NCRR), and human development (NICHD). Twelve members of the American Society of Neuroradiology are PIs on NIH-funded projects. By any standard, this performance is dismal, and it reflects a singular lack of focused research effort by our profession.

With the advent of MR imaging, fortune provided us with a powerful analytical instrument capable of investigating certain physiologic processes in the brain in vivo. The significance of this development has not been lost on neuroscientists from other disciplines. I believe it is unethical to withhold the use of a medical instrument from a researcher whose goal is to investigate a hypothesis that may reduce patient suffering. Provided that time is available on the instrument and the investigator is prepared to pay for this time, the instrument should not be withheld purely on the basis of ''turf'' issues. Neuroradiologists should be eager to collaborate with scientists from other disciplines who wish to initiate an investigation using MR imaging. Often they will come to us first with their ideas. By being helpful initially, we almost can assure ourselves a role in the project; otherwise, they may bypass us and ultimately co-opt the imaging scientists in our own department. We in neuroradiology should be prepared to collaborate enthusiastically with others by lending the project the benefit of our unique insight. Having said that, it is also of critical importance that we assume equal footing in our particular research communities by acquisition of research funding as PIs.

The field of medicine is in an unsettled state. Practice patterns are being altered by government policy and business decisions imposed by hospitals and insurance companies. Unit reimbursement for our skills is shrinking. We are being monitored to verify that, as faculty, we actually are involved in the performance of procedures that senior residents and fellows once managed as an important step along their training pathway. As a group, our response to these challenges has been to work harder, to interpret more studies, and to spend less time in intellectual and research pursuits.

Although the situation in medicine can be described as somewhat chaotic, in chaos there is opportunity. A singular opportunity exists over the next decade because of the recently passed Senate version of the Federal Research Investment Act, which calls for doubling federal civilian research support by the year 2010. It is said that $1.00 in start-up funds is needed for every $3.00 of ultimate grant support. I am not so optimistic. I believe that, after factoring in the capital expenditures associated with the instruments we use and the time lost from clinical activities, department expenditures must be closer to $2.00 for every $3.00 ultimately secured through grant funding. Departments that are running from hand-to-mouth on current clinical revenue will not have the resources to compete successfully for funding in this environment. My prediction is that the well-endowed departments, those with significant institutional support or reserve departmental funds, will benefit. The ranking of radiology departments will change in the next few years, in some instances dramatically, and those with inspired leadership will find it possible to leapfrog over a number of other established institutions.

By exhibiting initiative in the arena of funded research, neuroradiologists can directly influence the changes that will inevitably affect our profession.

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