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EDITORIAL

HIV Encephalopathy: On The Road to a Useful Diagnostic Test?

Future generations will look back on the AIDS epidemic as one of the most malicious mutations that nature has hurled at the human life form. Yet the course of the disease may play out differently from past plagues. Unless the virulence of HIV-1 takes another malignant turn, the extent of this disaster may be limited by changes in behavior and cultural values. The AIDS epidemic may also be muted by the galaxy of high technologies arrayed against it. If the ravages of AIDS are to be reduced before a vaccine is developed, diagnostic aides and effective therapeutic regimens must be developed. Diagnosis and therapy go hand in hand and it is often the development of the former that leads to meanful progress with the latter.

In an exciting study in this issue of the *Journal*, Masdeu et al. report on the accuracy of SPECT in the retrospective diagnosis of HIV-1 encephalopathy, the most frequent neurologic complication of HIV-1 infection (*1*). They found a high incidence of perfusion abnormalities even in patients with early disease (CDC Groups II and III) using [^{123}I]IMP SPECT. In a prospective study Schielke et al. reported similar results with ^{99m}Tc HMPAO SPECT (*2*). As promising as these studies are, we are only a short way along the road to documenting SPECT's clinical effectiveness.

The validation of any diagnostic test follows a path beginning with invention, standardization and description, leading ultimately to investigations of accuracy, cost effectiveness, and impact on patient outcome (*3*). While it is not possible to leapfrog directly to the multicenter trial or complex outcome studies before standardization, description, and early validation have taken place, it is vital that we not get bogged down on the way to clear answers.

The first reports of a new test typically compare its appearance in diseased patients and normal control subjects. If the test cannot distinguish between these two groups, it is too insensitive and there is no point to further testing. The specificity of a test must also be determined by taking into account other diseases which might mimic the one under study. Masdeu et al. are the first to address the specificity of brain perfusion SPECT for diagnosing HIV encephalopathy by including an abnormal control population. They found a clear separation in brain perfusion between patients with HIV encephalopathy and non-AIDS psychoses. Other confounding and overlapping processes will have to be considered in the future. Approximately 40%–60% of intravenous drug users are seropositive for HIV-1 antibody. Cocaine use among HIV-1 seropositive patients is at least as high as it is in the general population. Chronic polydrug use is associated with widespread focal cortical defects (*4*,*5*) which may be indistinguishable from the brain perfusion pattern seen in AIDS dementia.

The ultimate subject population for the validation of any diagnostic test must be an accurate replica of the population that will be referred to the test once it has been proved accurate. In the case of AIDS encephalopathy, that population will not include normal subjects and it will not include patients with non-AIDS psychosis. It will be a population made up entirely of HIV-1 seropositive patients. The usefulness of the test will hinge on its ability to distinguish HIV encephalopathy from other neurological complications such as opportunistic infections, metabolic encephalopathies, and vascular disorders and from those

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patients who do not, as yet, have active central nervous system infection. To prove that the diagnostic test is specific for HIV encephalopathy requires that we have an alternative method for judging the presence of the disease. It is called the reference standard.

At this point, we run into the central paradox of technology assessment research: the worse the reference standard, the more desperately we need a new diagnostic test. This paradox holds for AIDS encephalopathy. The HIV-1 gains entry into the central nervous system early in the course of HIV-1 infection. Patients remain asymptomatic while the virus lays dormant for a variable time. At some point, the virus awakens, creating an active encephalopathic process called HIV-1 dementia complex. When does the latent process become active and what is the relationship between histology and dementia? The incidence of the AIDS dementia complex during the various stages of the infection is unknown. Probably the majority of AIDS patients eventually develop cognitive symptoms if they survive long enough (*6*). Even the relationship between histologic appearance and dementia is unclear. Brew et al. suggest that only the presence of multinucleated cells are definitive evidence for brain infection (*7*). White matter pallor, with astrocytic proliferation and some mononuclear infiltration, is present in almost all AIDS patients. Other changes such as vacuolar myelopathy are seen in these patients but appear to be nonspecific and are unrelated to the encephalitic process per se. When strict histologic criteria are used, the infection may be limited to a few cells in patients with global dementia (*8*). Perhaps indirect mechanisms of injury play a role in the development of cognitive changes. Recent in vivo evidence demonstrates that the viral envelop glycoprotein gp120 (*9*) and neurotoxic agents secreted by infected macrophages (*10*) cause neuronal injury and death. Therefore, the pathophysiology of HIV dementia may not be caused by a single disease process but may involve a number of overlapping etiologies (*11*).

Both Masdeu et al. and Schielke et al. find perfusion changes very early in the course of the infection, in many cases before the patients develop significant cognitive impairments. Are we seeing brain image signs of cognitive impairment or are we seeing signs of viral infection that may or may not relate to cognitive changes? It may be premature to claim, as Schielke et al. do, that the test is defining "silent HIV encephalopathy," since uniform neuropsychological testing was not performed in either group. Consequently, mild cognitive and memory disturbances may have been undetected. Schielke et al. defined the HIV encephalopathy by the presence of oligoclonal IgG immunoproteins in the cerebral spinal fluid but these findings indicate only that the blood-cerebrospinal fluid barrier has become more permeable and may be seen in the latent phase of CNS infection as well as in active disease (*7*). Other disease endpoints such as clinical follow-up and autopsy results are unreliable because disease activity may change during the time interval between SPECT and follow-up.

All of these limitations suggest problems with the traditional measures of technology assessment and beg for alternative approaches. Recent shifts from accuracy to patient outcome measures have been advocated because it is ultimately the usefulness of a test that determines its worth (*12*). Patient outcome studies may also bypass some of the limitations of Bayesian analysis if the test becomes self-defining. If brain perfusion SPECT defines a subpopulation in which early treatment is warranted, and if that treatment is effective as Masdeu et al. and Brunetti et al. suggest (*1,13*), than it may be less important whether perfusion abnormalities precede encephalopathy or not. In fact, perfusion SPECT will have defined a more important boundary point than histology has thus far been able to do.

If perfusion SPECT is to play a useful role as a predictor of patient outcome and be useful in following therapy, qualitative visual image interpretation will not be enough. We agree with Masdeu et al. that a quantitative approach will prove more objective and more reproducible. However, the type of quantitation necessary is by no means clear. Absolute quantification of regional cerebral blood flow, while possible with single photon radiopharmaceuticals, would make the procedure far more complicated than would be acceptable for routine clinical use, since it would require arterial blood sampling, careful correction for attenuation, complex modeling of enzyme kinetics, and in vitro measurements of blood samples. The PET experience with absolute quantification of regional glucose utilization is not encouraging because of the wide variations that have been found in normal subjects. Relative indices have been more useful as diagnostic and treatment guides for both PET and SPECT. Recently developed techniques for computerized registration of structural and functional images (*14*) may clarify the pathogenesis of HIV encephalopathy. Does the white matter HIV lesion functionally disconnect overlying cortex, as has been proposed in other subcortical dementias such as progressive supranuclear palsy, multiple sclerosis, and Binswanger encephalopathy? It may be possible with MR/SPECT registered images to stratify patients according to severity by comparing MR white matter abnormalities with the functional status of overlying cortex.

Which radiopharmaceuticals and instrumentation to use for imaging HIV-1 seropositive patients must also be clarified. The abnormalities found at postmortem examination are often small, arguing for high-resolution systems. Masdeu et al. and others find high detection rates with the single-head gamma camera, but higher spatial resolution may be necessary in order to follow the disease process. If better image quality is needed, higher dose rates will be essential and ^{99m}Tc-

labeled compounds will be required. While Schielke et al. reported early detection of HIV encephalopathy with ^{99m}Tc HMPAO, slow blood clearance and in vitro instability may limit its use for quantitative serial studies. Technetium-99m-ECD may be the best compound for brain perfusion SPECT since it has superior imaging characteristics (*12*), but no detailed study describing its efficacy in AIDS has been reported at this time.

The usefulness of a test depends not only on its predictive value but also on its relative value. PET may be able to provide comparable information but it does so at a substantially greater cost. Conventional CT and MRI are not accurate indicators of early HIV encephalopathy but are indispensable for detecting opportunistic infections, neoplasms and hemorrhage (*15*). But, just as SPECT is evolving rapidly, other technologies are developing at an astonishing pace. Magnetic resonance spectroscopy, for example, can now measure high energy phosphate metabolites regionally in the brain. Deficits in brain phosphocreatine and nucleoside triphosphate have been identified in patients with HIV dementia. MRS could prove to be a reliable test for following disease progression and response to therapy (*17*). Any evaluation of the usefulness of brain perfusion SPECT will have to take into account alternative modalities.

Brain perfusion SPECT will play its greatest role in HIV encephalopathy when therapeutic choices are available. When a variety of therapeutic choices exist for these patients, a predictable and early test which also indicates the brain's response to therapy will be invaluable. In the meantime, a physiological test, which might unravel the diagnostic dilemma of early onset central nervous system involvement with HIV-1 infection, will not go unnoticed.

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