Continuing Education

SPECT Functional Neuroimaging in Patients with AIDS

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This is the third in a four-part article series on AIDS. Upon completion of this article, the technologist will have an understanding of the neurological complications of the AIDS virus and how nuclear medicine techniques can be used for early detection of CNS disorders.

It is currently estimated by the Centers for Disease Control (CDC) that between 1.5 and 2 million Americans have been infected with the HIV virus. The CDC also estimates that by 1991, ~250,000 AIDS cases will be documented (*1*). The consequential effect on society, both from the strain on the health care system and the fiscal impact of research and treatment has been dramatic and will likely become significantly worse in the future. The AIDS patient presents a complex situation in which for optimal care a dedicated response by all cross sections of the health care team, including those involved in diagnostic imaging, is necessary.

Brain imaging modalities such as computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single-photon emission computed tomography (SPECT) hold potential for early detection of AIDS-related Central Nervous System (CNS) disease and may also provide insight into the neuropathologic changes which occur in this disorder. Nuclear medicine may provide valuable diagnostic information with the application of new radiopharmaceuticals such as ^{123}I N-isopropyl-p-iodoamphetamine (iofetamine/IMP) and ^{99m}Tc-hexamethyl propyleneamine (HMPAO) utilized for SPECT brain studies to assess the neurologic manifestations of AIDS. Because of the development of these and other new radiotracers which reflect cerebral blood flow and with the continued technological advances in SPECT methodology, there has been a renewed interest in scintigraphic brain imaging. The widespread availability of SPECT imaging systems (as opposed to PET facilities) makes this technique very useful to the practicing clinician. SPECT functional neuroimaging is a technique which can provide three-dimensional information of brain perfusion/metabolism and, therefore, should be an effective, noninvasive method of evaluating pathophysiologic changes, which may occur in the brain associated with AIDS.

AIDS AND THE CENTRAL NERVOUS SYSTEM

AIDS represents a clinical syndrome in which opportunistic infections such as *pneumocystis carinii* pneumonia and malignancies such as Kaposi's sarcoma develop in the presence of suppressed cellular immunity. The immune system deficiency arises as a result of infection of the helper T-lymphocytes and macrophages by a retrovirus known as the human immunodeficiency virus (HIV). Not all individuals infected by the virus have the clinical signs and symptoms of AIDS. In some cases, a syndrome of weight loss, fatigue, and systemic lymphadenopathy will develop, which is referred to as the AIDS-related complex. In others infected by HIV, a rise in serum antibody titers to the virus may be present in the absence of any overt evidence of disease. While the exact percentage of patients in this category that will progress to develop the full-blown clinical picture of AIDS is not known, it has been estimated that from 15% to 40% of asymptomatic HIV sero-positive patients will develop AIDS within three years (*2*).

Neuropsychiatric symptomatology will eventually develop in the very large majority of patients with AIDS. Potential causes of CNS lesions in AIDS patients include infections with *Cryptococcus neoformans*, *Toxoplasma gondii*, or cytomegalovirus. In addition, brain involvement may occur with AIDS-related malignancies, the most common being primary CNS lymphomas. However, a large percentage of cases exist where neurologic abnormalities develop as a direct result of HIV infection in brain tissue (*3*). In such cases, the virus infects the brain somewhat diffusely, involving primarily white matter and subcortical nuclei with lesser degrees of involvement seen in cortical gray matter (*4*). It has been estimated that nearly two thirds of patients with AIDS will eventually develop this complication (*5*). Of interest, HIV-infected macrophages may play a role in the pathogenesis of the CNS disorder by transporting the virus to the brain and releasing various factors, which lead to inflammation and local neuronal damage (*2*).

Manifestations of direct CNS involvement with HIV include cognitive deficits, memory loss, and psychomotor slow-

ing, often referred to as AIDS dementia complex. Focal extremity weakness, ataxia, and tremor may also develop in some cases. While these findings are usually present in patients with other clinical symptoms associated with AIDS, in some cases neurologic abnormalities may develop as the initial manifestation of the syndrome. For example, in one study where 13 of 15 patients with AIDS had neuropsychiatric abnormalities, an additional 7 of 13 patients who were seropositive for HIV had neuropsychiatric findings without any other symptomatology (3).

Noninvasive medical imaging techniques have revolutionized the diagnosis and management of neurologic disorders in general, and evaluation of CNS lesions associated with AIDS is possible using any one of several of these imaging techniques. CT and MRI represent excellent methods of detecting AIDS-related opportunistic brain infections or CNS malignancies (6). However, for identifying direct brain involvement with HIV, CT has significant limitations. Specifically, CT may not be a sensitive technique for detecting early CNS infection with HIV. In such cases, MRI has proven to be of benefit showing positive results when CT is negative particularly in cerebral white matter (7). As is often the case in other CNS disorders, it is reasonable to expect that functional changes will occur prior to anatomic changes in the brain in cases of HIV infection. Consequently, physiologic imaging techniques such as SPECT and PET may prove to be even more sensitive than other modalities in evaluating these patients. An analogous situation is found in patients with Alzheimer's type dementia, since it appears that SPECT functional neuroimaging will often identify abnormalities in this disorder in advance of definitive changes seen on CT or MRI.

SPECT NEUROIMAGING CONCEPTS

SPECT imaging represents a method in which scintigraphic data is acquired and processed to reveal the three-dimensional distribution of gamma emitting radiopharmaceuticals within a certain organ system. In the brain, SPECT imaging is most often performed using a rotating gamma camera. Because of its modest cost and substantial versatility, this instrument has become a mainstay in the modern nuclear medicine department and is widely available throughout the country. However, dedicated SPECT multidetector imaging rings are being marketed, which provide moderately improved resolution compared to rotating gamma cameras. It remains to be seen whether the added costs and limited scope of these instruments will be justified by the modest improvement in image resolution.

The recent development of a large group of single-photon emitting lipid soluble (lipophilic) radiopharmaceuticals, which readily cross the blood brain barrier, has generated tremendous enthusiasm for functional assessment of the CNS using SPECT imaging. The radioiodinated compound iofetamine was first marketed in 1988 followed by ^{99m}Tc-HMPAO, which received FDA approval approximately one year later. A variety of other investigational agents are cur-

rently being evaluated and it is expected that an ever increasing number of SPECT brain imaging radiotracers will become available in the future.

Iofetamine distributes in the brain after i.v. injection in direct relation to regional cerebral blood flow (rCBF) and, in addition, localization of this molecule is determined by binding nonspecifically to various types of amine receptors on metabolically active synaptosomes (8). The initial brain distribution of this agent remains fairly stable for ~15-60 min postinjection, making SPECT imaging with a rotating gamma system feasible during this period. Thereafter, a redistribution phenomenon occurs in which the tracer concentration dependence on blood flow is lost with the result being a delayed pattern of uptake probably reflecting the presence of functional synaptasomal receptors. It has been suggested that imaging of the late iofetamine brain distribution may provide unique information on the viability state of neuronal tissue (9). Technetium-99m-HMPAO is also strongly dependent on rCBF for initial brain distribution after i.v. injection, but unlike iofetamine no significant tracer redistribution occurs after the first 10 min postinjection. This may be due, in part, to the different mechanism of cerebral retention whereby upon entering the brain tissue HMPAO spontaneously breaks down to a polar compound which cannot diffuse back across the blood brain barrier. In addition, while the lungs act as a reservoir for iofetamine slowly releasing this tracer over time and contributing to the redistribution, no such pooling phenomenon occurs with HMPAO. In many clinical settings, the results obtained with SPECT are found to be very similar for these two agents. Nevertheless, there are situations in which significant differences may occur in the results obtained from these different radiopharmaceuticals and the determination of which to use in a particular clinical setting has yet to be ascertained. In particular, the clinical significance of the iofetamine redistribution phenomenon merits close attention.

Technical precision in data acquisition is crucial in obtaining high quality SPECT images. To perform SPECT neuroimaging with iofetamine, the patient is injected with 4-5 mCi (148-185 MBq) of the tracer. This injection is done in an isolated room, which is kept darkened and free from excessive external stimuli (i.e., light, noise, movement). The patient is instructed to remain quiet with eyes open for 15 min postinjection. These steps help to assure that regional blood flow variations to the brain that might be caused by the aforementioned stimuli (and which could lead to image interpretation errors) are minimized. The patient is placed on a SPECT imaging table and the head is secured with a velcro strap or elastic bandage in a head holder attached to the table. Imaging is performed using a rotating gamma camera* with a dedicated computer system for data collection and reconstruction. A high resolution low-medium energy microcast collimator designed for ^{123}I imaging is utilized at our institution. However, a low-energy, general-purpose collimator will also provide good quality images. An energy centerline of 159 keV and a window of ± 10% is used. This energy acceptance window is used in an effort to obtain high statistical counts while minimizing scatter radiation in the image. A zoom of

1.6–1.7 with an electronic offset is used to center the image in the lower, middle 1/3 of the crystal. We use a 64 × 64 byte mode continuous SPECT acquisition and acquire data each 3° over a total arc of 360° (120 projections). However, the step and shoot method of acquisition is an acceptable alternative. A 30-min data acquisition time will result in a total count collection of 1–2 million counts over the entire study, depending on the particular collimator specifications. Delayed imaging may also be performed as clinically indicated 3–4 hr postinjection when using iofetamine.

Some variations in imaging technique are required when using 99mTc-HMPAO versus 123I iofetamine. For example, 10–20 mCi (370–740 MBq) of 99mTc-HMPAO is normally used as compared to the usual 4–5 mCi dose of iofetamine. Again the injection is performed in an isolated quiet room where the patient remains for only 5–8 min prior to initiating imaging. The shorter duration of time for HMPAO between injection and onset of imaging is made possible by the rapid attainment of peak brain activity with this agent. The patient is placed on the SPECT table and the head is securely held in position. A high resolution low-energy collimator is desirable, but a low-energy general purpose collimator will also provide excellent quality images. The energy centerline should be at 140 kev with a ± 10% window. A 15–30 min acquisition should result in ~2.5–5 million total counts. The possibility of using shorter acquisition times with HMPAO may be very useful when imaging an uncooperative or demented patient where head motion can be a problem. All other acquisition parameters remain constant from the iofetamine imaging. However, delayed images are not obtained.

Framed data should be normalized for center of rotation, isotope decay, and time/frame to compensate for variations in gantry speed. A high count uniformity correction map should also be applied to limit nonuniformities to a range of 1%–2%. If this is not achieved, ring artifacts may appear in the reconstructed images. Transaxial slices of two pixel thick-

ness (0.8–1 cm/slice) are reconstructed through the entire brain mass. A system optimized Metz or other resolution recovery filter is recommended when available. However, a Parzen or similar "low-pass" backprojection filter will yield acceptable image quality when applied in the reconstruction process. After reconstructing the transaxial slices, it is important to generate sagittal, coronal, and transaxial/oblique slices. The transaxial/oblique slices are obtained by defining a set of planes on the sagittal projection, which run parallel to a line through the inferior aspect of the frontal lobe and the cerebellum. Defined in such a way, these transaxial/oblique slices are approximately parallel to the canthomeatal line and usually represent roughly a 5–10-degree offset from the original transaxial cross-sections depending on the way in which the head is angled in the head holding device. The final oblique images are 9 point spatially smoothed and presented for interpretation in a sequential image organization from the base to the apex of the brain.

SPECT NEUROIMAGING FINDINGS

SPECT images with 123I iofetamine or 99mTc-HMPAO in normal individuals show highest tracer concentrations in the cerebral cortical gray matter, subcortical gray matter (thalamus and basal ganglia), and cerebellum. The cerebral white matter generally has blood flow levels roughly 3–4 times less than cortical gray matter leading to correspondingly lower tracer accumulation in this region of the brain. Visualization of the deeper cerebral gray matter nuclei such as thalamus and basal ganglia may be enhanced by applying attenuation corrections to the SPECT data. The Chang method utilizes a postreconstruction attenuation correction which is relatively simple to apply. This technique assumes a uniform tissue density and requires the operator to choose an attenuation coefficient which for the brain is often taken as 0.11 or 0.12/cm. In general, there should be good right to left symmetry seen on images from normal subjects with count rate asymmetries of > 10% likely indicating the presence of pathology. If the images are displayed on a CRT with multilevel color scale, a visual estimate of the degree of symmetry can be obtained. However, more precise determination of symmetry would require computer placement of regions of interest around selected brain structures to obtain the right to left ratios. Figure 1 shows transaxial/oblique slices using iofetamine from a normal individual with no cerebral pathology. Notice from this image set the much higher count density in the outer cortex relative to the inner cerebral white matter. Tracer distribution in normal brains will depend on sensory input which is why it is important to standardize the external environment conditions for SPECT brain imaging within a given nuclear medicine department.

It is often instructive to review results from PET imaging when considering what SPECT imaging will reveal in a particular disease state. A recent study of patients with AIDS-related neurologic symptoms using PET measurements of regional brain glucose to map cortical metabolism found areas of cortical and subcortical hypometabolism on the PET im-
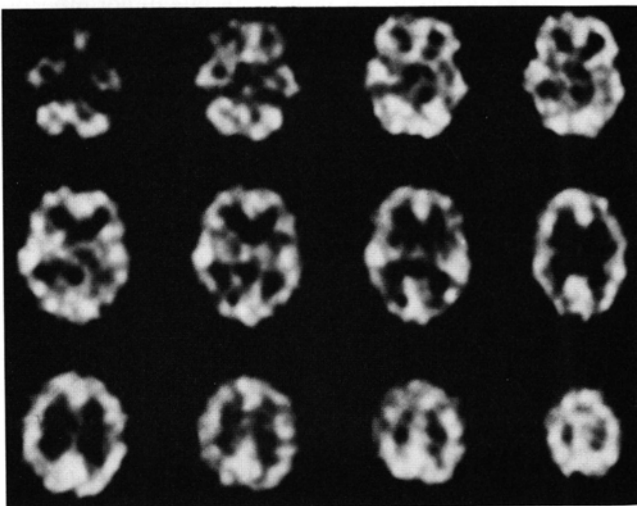

FIG. 1. Normal transaxial/oblique images of base (top left) to apex (bottom right) from SPECT iofetamine study demonstrating increased activity in outer gray matter and cerebellum with good right to left symmetry.

ages (10). To date, there has not been a great deal of reported experience with SPECT neuroimaging in cases of HIV infection of the brain. However, from the limited reports in the recent literature, SPECT studies appear to show (similar to what has been seen with PET) focal areas of reduced metabolism/perfusion in cases of AIDS dementia (11). These abnormalities on SPECT may be single or multiple and may be present almost anywhere in the brain. In addition, abnormalities on SPECT images may be seen in some HIV seropositive patients prior to the onset of clinical neuropsychiatric symptoms (12). An example of a SPECT/iofetamine image from an HIV positive patient with the AIDS-related complex and moderate dementia is shown in Figure 2. Notice the multiple areas of reduced iofetamine activity in the frontal lobes bilaterally and left posterior parietal region. SPECT neurofunctional imaging may well be a very sensitive (albeit probably nonspecific) method of detecting brain involvement in HIV positive patients. In the study by Pohl et al., all 12 patients with AIDS-related dementia had at least one abnormal region on SPECT images (11). It would be very helpful in managing AIDS patients if SPECT were able to identify which individuals were at risk for developing dementia while still in the asymptomatic phase. However, questions such as these will require further investigation with controlled prospective clinical studies.

Other neuroimaging techniques have been employed in the evaluation of brain pathology in patients with AIDS. When focal infections or tumors are present in such patients, the CT and MRI images will show focal space occupying lesions in the brain. In cases where HIV brain infection has led to dementia, CT and MRI images often show diffuse cerebral

FIG. 2. Single transaxial SPECT iofetamine image from a patient with ARC and dementia showing multiple focal defects in frontal and left posterior parietal regions (arrows). (Reprinted by permission from Pohl P, Vogl C, Fill IT, et al. Single photon emission computed tomography in AIDS dementia complex. *J Nucl Med* 1988;29:1382–1386.

cortical atrophy and no other abnormality. However, in some cases T_2 weighted MRI images will demonstrate signal enhancing lesions in the subcortical white matter (7).

SPECIAL CONSIDERATIONS

The AIDS patient presents a special situation to the health care worker. Universal precautions during the performance of SPECT neuroimaging should be utilized for all patients as HIV infection may be undetected in some individuals. Gloves should be worn when performing any venipuncture or injection of radiopharmaceuticals (13). Additional safety equipment such as gowns and face masks may be required as the situation dictates. These considerations should be discussed with the infection control team within the individual institution. As previously discussed, many AIDS patients may present with manifestations of dementia or other motor function abnormalities. Severely uncooperative or demented patients may be unable to sustain a motionless position long enough to complete the study. In such cases, sedation may be prescribed by the responsible physician as deemed appropriate to assist in maintaining patient compliance during the imaging procedure.

Other technical considerations for SPECT brain imaging include the use of a truncated circular head gamma camera or a square/rectangular instrument to allow clearance of the patient's shoulders thus achieving a smaller radius of rotation. The close proximity of the collimator surface to the patient's head is critical for optimal resolution in the SPECT brain images. The head must be held securely and motionless over the entire procedure for good quality images. A well designed head holder attached to the SPECT table is invaluable in accomplishing this most important task. Procedures as simple as securing the patient's head with an elastic Ace bandage or soft neck collar may be very helpful in this regard.

Camera quality control is extremely important. A good center of rotation correction must routinely acquired for effective SPECT imaging. A high count rate uniformity correction map (30 million counts) should be acquired weekly using the acquisition parameters utilized in the actual patient study (i.e., acquisition zoom and UFOV offset). Actual experience in performing these brain imaging techniques is the best formula for success. The appropriate and most effective methods must be determined by each laboratory independently for the best combination to achieve optimal results. Finally, it should be noted that ^{123}I-iofetamine should not be administered to patients who are currently using monoamine oxidase (MAO) inhibitor drugs, which are used on rare occasions to treat certain psychiatric conditions, since the combination may cause extreme rises in these patients blood pressure.

CONCLUSION

Neurologic manifestations are an unfortunately common and devastating complication of the HIV virus infection. Identification of CNS disease with medical imaging techniques in AIDS patients can be very helpful in caring for these
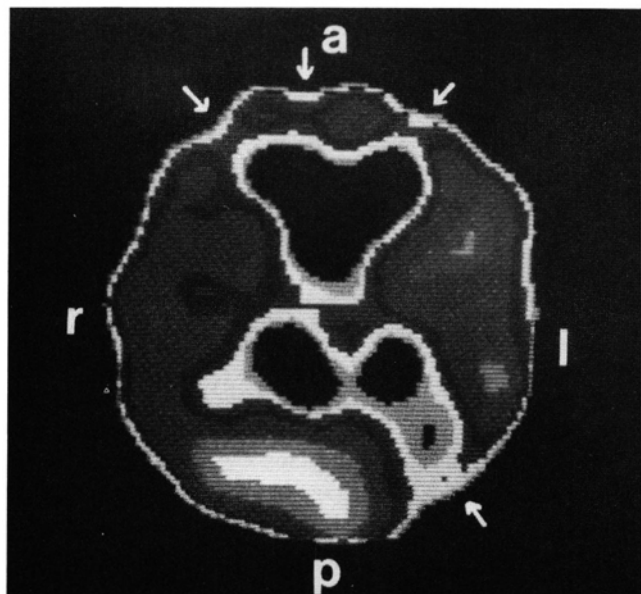
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individuals. Early detection of HIV brain involvement will become increasingly more important as better methods of therapy are developed in the future. SPECT functional neuroimaging may be a sensitive method for evaluating CNS involvement of the HIV virus. However, the precise role for this imaging technique in the work-up of AIDS patients has yet to be defined.

NOTE

*Apex 415, Elscint Inc., Boston, MA.

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SPECT FUNCTIONAL NEUROIMAGING IN PATIENTS WITH AIDS

For each of the following questions, select the best answer. Then circle the number on the reader service card that corresponds to the answer you have selected. Keep a record of your responses so that you can compare them with the correct answers, which will be published in the next issue of the *Journal*.

A. *The current estimated number of Americans infected with the AIDS virus is:*
101. 1.0–1.5 million.
102. 1.5–2.0 million.
103. 2.0–2.5 million.
104. 2.5–3.0 million.

B. *In normal individuals, the tracer uptake of functional neuroimaging agents is greater in the:*
105. white matter.
106. cerebellum.
107. cortical gray matter.
108. subcortical gray matter.
109. 106, 107, and 108.

C. *As a direct result of the HIV infection to the brain, primarily the white matter and subcortical nuclei are involved and never the gray matter.*
110. True
111. False

D. *Central nervous system symptoms in patients with AIDS may result from:*
112. focal infection.
113. malignancy.
114. diffuse infection.
115. all of the above.

E. *Of the patients with AIDS, it is estimated that the percentage who will develop CNS complications is:*
116. <10%.
117. ~25%.
118. ~66%.
119. ~100%.

F. *AIDS dementia complex includes:*
120. cognitive defects.
121. memory loss.
122. psychomotor slowing.
123. all of the above.

G. *Focal areas of reduced metabolism/perfusion in HIV seropositive patients may be seen prior to the onset of symptoms.*
124. True
125. False

H. *The use of ^{123}I-iofetamine is contraindicated in patients:*
126. using MAO inhibitor drugs.
127. who are well hydrated.
128. previously studied with ^{123}I-iofetamine.
129. none of the above.

I. *CT and MRI images often show diffuse cortical atrophy when:*
130. HIV brain infection has not led to dementia.
131. multiple other abnormalities are present.
132. HIV brain infection has led to dementia.
133. focal lesions are present.

J. *Initial brain distribution of iofetamine remains fairly stable for _____ postinjection.*
134. 30–120 min
135. 15–60 min
136. 2 hr
137. 5 hr

K. *After the initial SPECT brain study, a follow-up SPECT study may be performed 3–4 hr later when using ^{99m}Tc-HMPAO.*
138. True
139. False

L. *To minimize regional blood flow variations for ^{123}I-iofetamine, patients are:*
140. instructed to remain quiet for 15 min postinjection.
141. told to keep their eyes open for 15 min postinjection.
142. told to keep their eyes closed for 15 min postinjection.
143. isolated in a dark room for 15 min postinjection.
144. 140, 142, and 143.

Your answers to the above questions should be returned on a reader service card (found in the back of the *Journal*) no later than December 1, 1989. Remember to supply your name and address in the space provided on the card; also, write your VOICE number after your name. Your VOICE number appears on the upper left hand corner of your *Journal* mailing label. No credit can be recorded without it. A 70% correct response rate is required to receive 0.1 CEU credit for this article. Members participating in this continuing education activity will receive documentation on their VOICE transcript, which is issued in March of each year. Nonmembers may request verification of their participation but do not receive transcripts.

Answers to CE Article Tests, June 1989

The Continuing Education article in the June 1989 issue, "Management in the Current Health Care Environment," by Howard W. Schwartz was accompanied by a CE article test. The correct answers are:

A.	101	D.	111	G.	120	J.	127	M.	135
B.	104	E.	114	H.	121	K.	129		
C.	107	F.	115	I.	125	L.	133		

The answers to the CE article test on "Care of the Person with Human Immunodeficiency Virus-Related Opportunistic Disease," by Suzanne Shaffer are:

A.	137	D.	145	G.	153	J.	163	M.	172
B.	140	E.	147	H.	155	K.	168	N.	175
C.	142	F.	148	I.	160	L.	170		

Erratum

Answers to questions in the December 1988 CE tests were printed incorrectly. Correct answers are as follows: "Care and Management of the AIDS Patient," by Geraldine Grandberry: A. 104; N. 143. "Collimator Technology and Advancements," by Robert J. Wilson: B. 159.