White Matter Ischemia on Brain SPECT

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Four patients were shown to have ischemic injury to the posterior limb of the internal capsule on brain SPECT with ^{99m}Tc-HMPAO. These findings were later corroborated by transmission CT scans in three patients. In the interpretation of high-resolution SPECT imaging of regional cerebral blood flow, it is important to inspect the deep white and gray matter activity for asymmetry and perfusion deficits. The blood flow to the diencephalon, which is critical for brain function, can be imaged with high-resolution brain SPECT. The early ascertainment of ischemic changes in the diencephalon may lead to important patient management decisions.

Key Words: white matter; internal capsule; ischemia; technetium-99m-HMPAO; SPECT

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SPECT imaging of regional cerebral perfusion has been used to detect zones of ischemia and infarction early in acute cerebrovascular disease (*1*). Because brain perfusion radiopharmaceuticals label the gray matter in preference to white matter approximately 1.7:1 (*2–5*), the findings ascribable to white matter changes are generally less obvious than those in gray matter. Nevertheless, ischemic changes in white matter may often affect gray matter perfusion via neuronal deafferentation, a subtype of diaschisis, which may be detected by SPECT (*6*). Diaschisis is functional impairment distant from a site of anatomical brain injury due to disruption of neuronal pathways, whereas deafferentation specifically refers to functional inactivation of the cortex due to axonal injury present in white matter lesions (*7*).

SPECT is not sensitive for infarcts in the brain stem but does detect diaschisis due to brain stem lesions (*8*). In the interpretation of high-resolution brain SPECT, it is important to pay attention to zones of the brain that most nuclear medicine practitioners have not focused on before, such as deep white matter tracts, and to look for the effects of diaschisis/deafferentation from the white matter lesion(s) on the cortex. Correlation with CT or MRI techniques that are more commonly used to evaluate white matter ischemia can help clarify white matter localization of SPECT abnormality. De Roo et al. noted that deep white matter or deep gray matter ischemic changes were sources of false-negative findings on high-resolution SPECT compared to CT (*9*). We present four cases of posterior limb internal capsule ischemic changes detected by brain SPECT.

CASE REPORTS

Patient One

A 49-yr-old female had surgical clipping of a basilar tip aneurysm which had caused subarachnoid hemorrhage. She had poor responsiveness on the first postoperation day. SPECT was performed 1 hr after intravenous administration of 30 mCi (1110 MBq) of ^{99m}Tc-hexamethyl-propyleneamine oxime (HMPAO, Ceretec, Amersham/Medi-Physics, Arlington Heights, IL) was performed with a triple-head gamma camera (Prism 3000, Picker, Bedford Heights, OH). Low-energy, high-resolution parallel-hole collimators were used for the acquisition at 25 sec/stop over 120 stops. The images were processed with a Wiener pre-filter and ramp backprojection with boundary method attenuation correction. Displayed slices on a 128 × 128 matrix were 6.68 mm thick. CT results were not evaluated prior to the SPECT interpretation. SPECT showed mild left-posterior temporal and adjacent parietal hypoperfusion and a right inferior fronto-temporal operative site abnormality.

A second SPECT was performed on the next day because the patient's clinical status had not improved. The second SPECT showed new marked hypoperfusion (which in retrospect was seen as very mild early changes on the first scan) in the left posterior limb of the internal capsule and adjacent thalamus in the lateral and inferior aspects, and in the right posterior limb of the internal capsule and adjacent thalamus positioned more inferiorly. The left posterior temporal and adjacent parietal mild hypoperfusion had resolved. CT results, obtained after the SPECT interpretation, correlated with the findings of deep gray/white matter injury on brain SPECT. Region of interest (ROI) analysis showed a left-to-right ratio (L/R) of 0.84 on the first scan and a L/R of 0.78 on the second scan. The side-to-side asymmetry index (SAI) was 16.5% on the first scan and 20.5% on the second scan (see Appendix for equations) (Fig. 1).

Patient Two

A 60-yr-old female had a left internal carotid artery ligation in 1978 for a giant left internal carotid artery aneurysm. Presently, she underwent clipping of the aneurysm and had brain SPECT performed on the first postoperation day. SPECT showed left inferior fronto-temporal operative site hypoperfusion, mild bilateral occipital lobe hypoperfusion, a central photopenic defect in the region of the inferior deep frontal region corresponding to the

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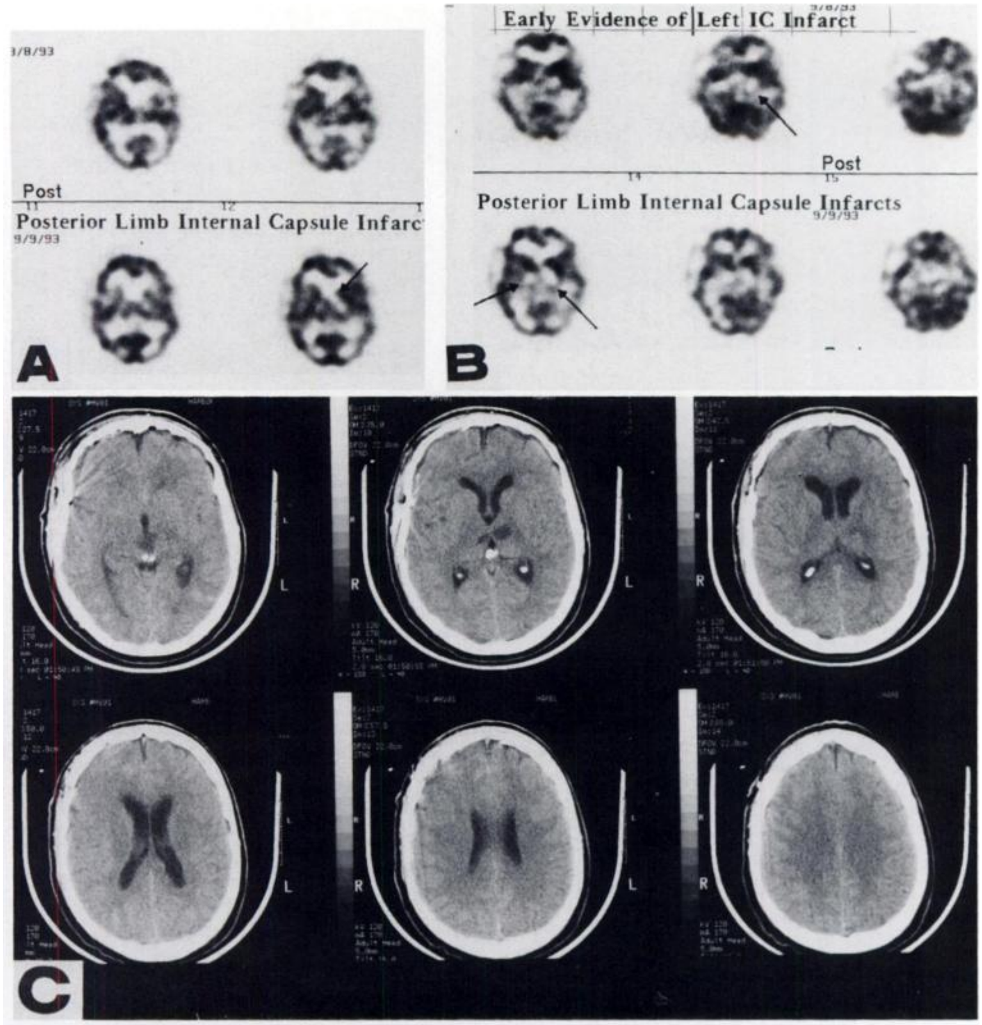

FIGURE 1. (A and B). Transaxial SPECT for Patient 1 on the first postoperative day (top) and the second postoperative day (bottom). Note early evidence of left posterior limb of the internal capsule and thalamic infarcts on the top, middle image denoted by the arrow in (B). Images on Day 2 show more convincing bilateral ischemic injuries denoted by arrows. Defect in the right inferior fronto-temporal region in the last image on the upper row of (B) is the operative site. There is also mild left orbito-frontal hypoperfusion. Mildly increased soft-tissue uptake on the right is reflective of expected scalp activity from recent craniotomy. There is a slight right-to-left head tilt on the second study, but the defects seen in multiple views are not caused by the tilt (software unavailable for tilt correction or more precise coregistration). (C) Noncontrast head CT scan performed on the same day as the second SPECT shows bilateral hypodensities, left greater than right, in the thalami and adjacent white matter.

giant aneurysm and a perfusion defect in the posterior limb of the internal capsule on the left. ROI analysis showed a L/R of 0.79 and a SAI of 27.9%. CT showed the infarct in the posterior limb of the internal capsule to be new compared to preoperative CT scans. The infarct measured 1.5 cm × 2.0 cm × 8 mm (Fig. 2).

Patient Three

A 40-yr-old female had undergone left parietal arteriovenous malformation (AVM) resection 7 days previously. Because of a lack of neurologic improvement and right hemiparesis, SPECT was performed to evaluate regional cerebral perfusion. The scan showed an absolute defect in the left superior parietal region at the site of AVM resection with adjacent mild-to-moderate hypoperfusion in the posterior temporal and inferior parietal regions. In addition, there was severe hypoperfusion in the posterior limb of the internal capsule on the left. ROI analysis showed a L/R of 0.69 and a SAI of 31.2%. CT showed low density in the left temporoparietal cortex extending deeply into the white matter and into the posterior limb of the internal capsule (Fig. 3). This finding was probably related to venous infarction.

Patient Four

A 34-yr-old female suffered a subarachnoid hemorrhage due to a basilar tip aneurysm. Approximately 5–7 days after aneurysm clipping, the patient developed progressively severe vasospasm of the basilar artery with associated neurologic findings including obtundation. SPECT was performed prior to cerebral angiography and showed right thalamic hypoperfusion and adjacent posterior limb of the internal capsule hypoperfusion which were not found in previous scans. After cerebral angiography was performed, the patient was treated with intra-arterial papaverine (300 mg) instilled by catheter into the basilar artery. SPECT on the subsequent day showed moderate resolution of the hypoperfusion in the right thalamus and internal capsule (Fig. 4). CT did not demonstrate ischemia in these areas during the interval of severe vasospasm and treatment. ROI analysis showed a L/R of 1.13 on the first scan and 0.99 on the second scan. SAI was −17.6% on the first scan and 2.5% on the second scan.

DISCUSSION

Imaging of the diencephalon has not been the primary focus of brain SPECT and has been generally considered the domain of CT and, more prominently, MRI. However, just as SPECT imaging of the neocortex has been employed to detect the earliest changes of acute cerebrovascular disease in preference to the anatomic modalities, the availability of state-of-the-art, multidetector and brain-dedicated systems for nuclear tomography has enabled nuclear medicine practitioners to see deep gray and white matter ischemia, something not seen before with single photon-emitting brain radiopharmaceuticals. The measured (in air)

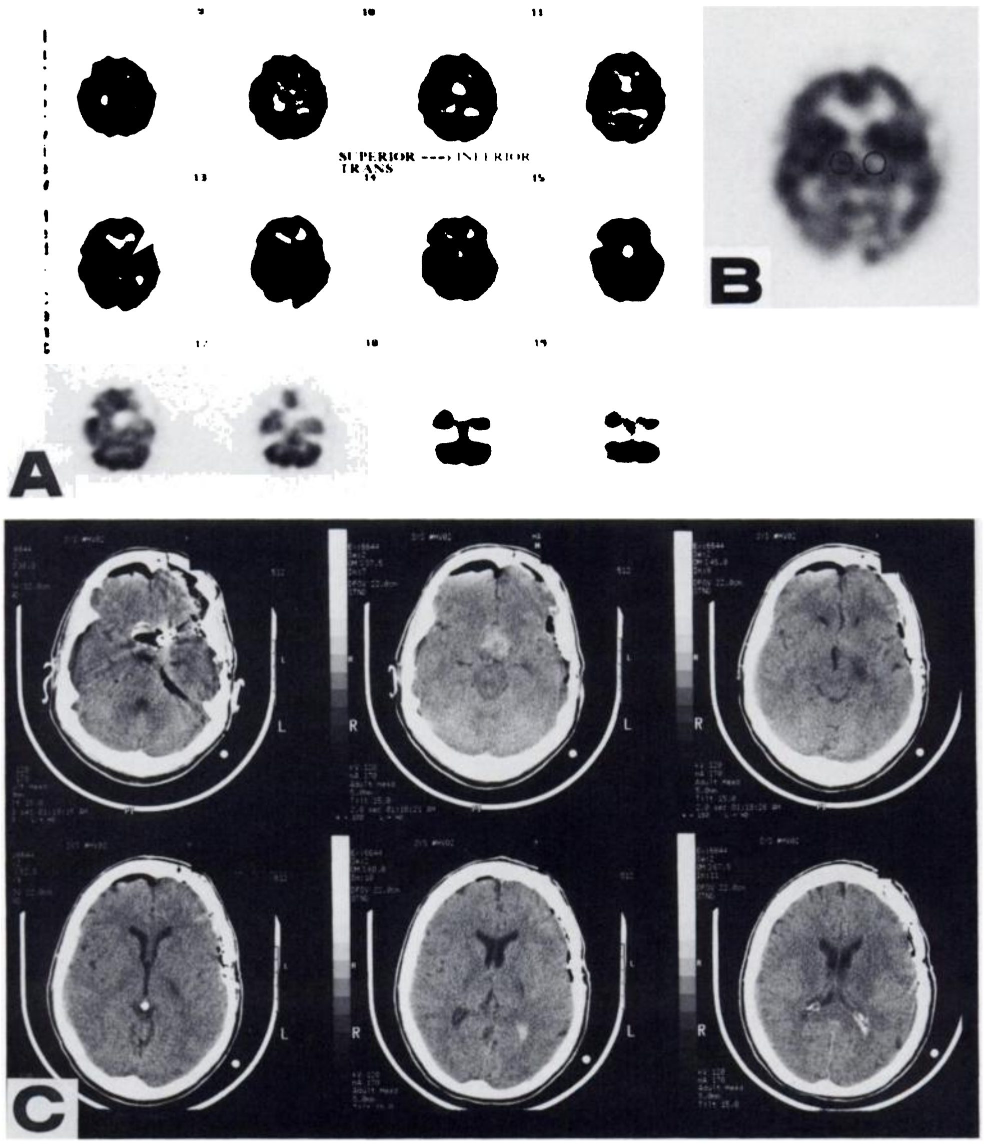

FIGURE 2. (A) Transaxial SPECT for Patient 2 shows marked hypoperfusion of the left posterior limb of the internal capsule (white arrow) on the first postoperative day after clipping of a giant aneurysm. Midline photopenic defect seen best on the last image in the middle row is the site of the giant aneurysm. Defect in the left inferior front-temporal region is the operative site. (B) ROI placement for Patient 2 for left versus right statistics. (C) Noncontrast head CT scan performed on the same day as the SPECT shows hypodensity in the posterior limb of the internal capsule on the left.

SPECT spatial resolution at full-width half-maximum of our institution's Prism 3000 system equipped with low-energy, high-resolution parallel-hole collimators at a detector radius of 16.5 cm was 8.8 mm at the center of the field of view in the transverse axial plane. Therefore, with this spatial resolution, gray matter lesions can be easily seen. However, the ability to obtain more counts with three detectors in a reasonable scanning time has improved the tomographic statistics and yielded excellent contrast (with the appropriate processing filter), allowing the nuclear medicine physician to detect a photopenic lesion in an area of much less uptake than the gray matter, such as in the posterior limb of the internal capsule which our cases have demonstrated. Use of low-energy, ultrahigh-resolution fan-beam collimators should improve lesion detectability as well.

The normal variability of the deep gray nuclei and white matter tracts on brain SPECT needs to be defined before making definitive statements on the significance of detected asymmetries. Our institution as yet does not have a normal database for this analysis. Waldemar et al. reported semiquantitative SAIs in 53 normal patients from age 21 to 83 yr (*5*). For the thalamus, the range of 2 standard deviations in normals was from −17.2% to 17.6%. For the lenticular nucleus it was −12.3% to 12.9%, and for the centrum semiovale (the only white matter area quantified in their study) it was −13.0% to 11.1% (*5*). The SAI values for the posterior limb of the internal capsule are not available from this group's work, but the SAI values calculated from ROI analyses of our cases appear to exceed, by 2 standard deviations, the reported range of normal values for the centrum semiovale, a comparable white matter zone.

The diencephalon's blood supply comes from the vertebro-basilar artery for a posterior part of the diencephalon, the posterior communicating arteries which supply the anterior thalamoperforating branches to the anterior and medial parts of the thalamus, and the posterior cerebral arter-

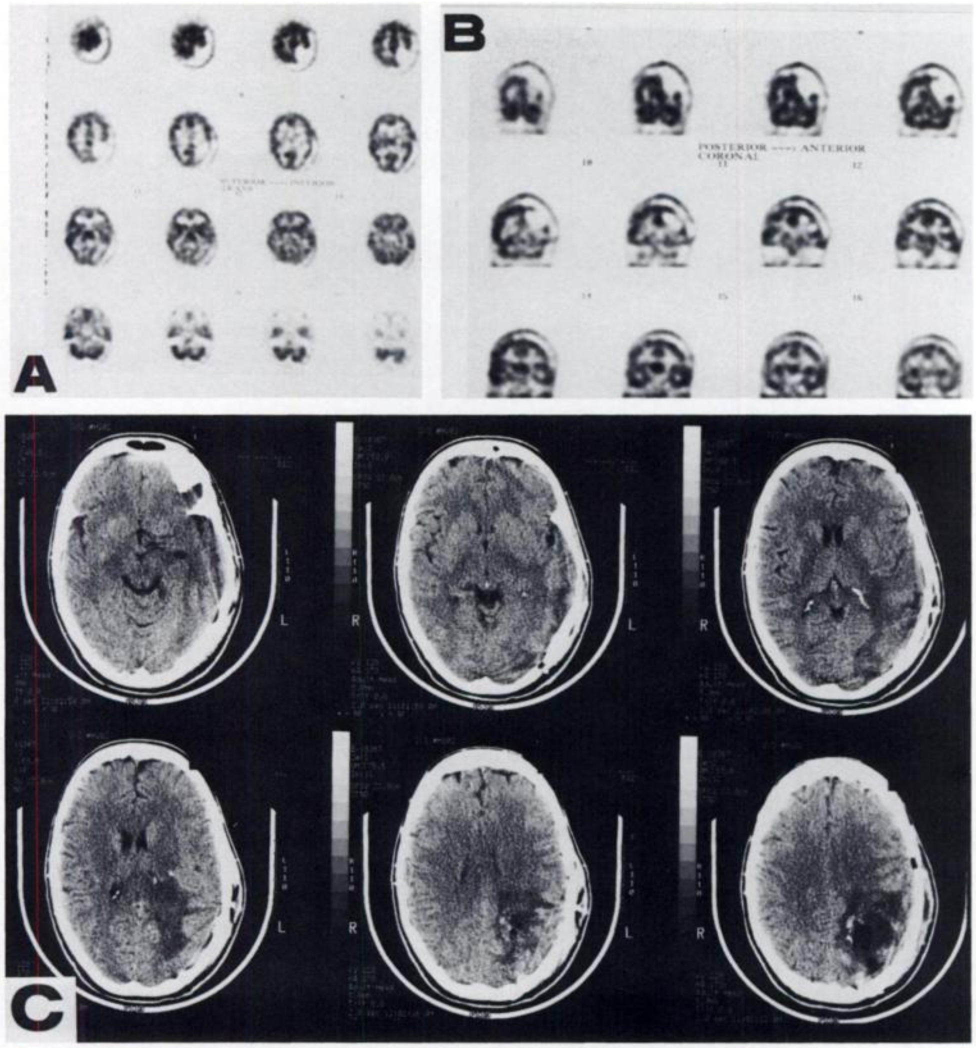

FIGURE 3. (A) Transaxial SPECT for Patient 3 shows a large photopenic defect at the site of resected AVM in the left parietal region. Hypoperfusion extends inferiorly and mesially to involve the posterior limb of the internal capsule on the left best seen on the last image of the second row and first image of the third row. (B) Coronal SPECT images for Patient 3 show clear involvement of the posterior limb of the internal capsule on the left, seen on the last row of images. (C) Noncontrast head CT scan shows left-sided white matter hypodensity that extends into the posterior limb of the internal capsule.

ies which supply the posterior thalamoperforating arteries and thalamogeniculate branches to the caudal half of the thalamus (*10*). These vessels also feed the adjacent white matter. In clipping posterior communicating and basilar tip aneurysms, it is likely that violated branches include the thalamoperforating arteries (*11*). Therefore, the neurological surgeons who perform these operations are most interested in the postoperative perfusion to the thalamus. Also, vasospasm which occurs after subarachnoid hemorrhage (SAH) may affect these posterior circulation vessels and result in delayed ischemia to the deep nuclei and white matter structures of the diencephalon. Early detection of vasospasm-induced ischemia followed by interventional treatment has improved the outcome in affected SAH patients (*12,13*).

New camera systems and radiopharmaceuticals are opening doors for nuclear medicine. They are also challenging us to review neuroanatomy in a new context and shedding light on the pathophysiology of the brain. Our systems as yet cannot resolve the primary lesions that MRI may show in the mesencephalon, pons and medulla (*8*). However, no competing anatomic imaging technique can demonstrate the secondary and distant effects of cortical, subcortical or white matter injury in the form of diaschisis, a functional disturbance due to disconnection. These findings, unique to functional brain imaging, may explain why there are some significant difficulties in clinically distinguishing lacunar from cortical strokes.

As treatment protocols for acute cerebrovascular disease, including techniques of interventional neuroradiology, come forth, we will be asked what we can see and how soon we can see it. There is some controversy over the accuracy of differentiating lacunar states from nonlacunar strokes by the clinical neurologic exam (*14,15*). Interventional treatment protocols will rely heavily on the ability to accurately define stroke subtypes. Therefore, imaging will play a critical role in stroke intervention, and high-resolution SPECT is ideally suited to image the presence of ischemic injury, to potentially subtype the injury and to monitor response to therapy (*16,17*). Due to the small number of cases presented and the lack of a complete database for perfusion asymmetries in normals, no statement as to the sensitivity or specificity of deep gray/white matter lesions can be made without amassing large num-

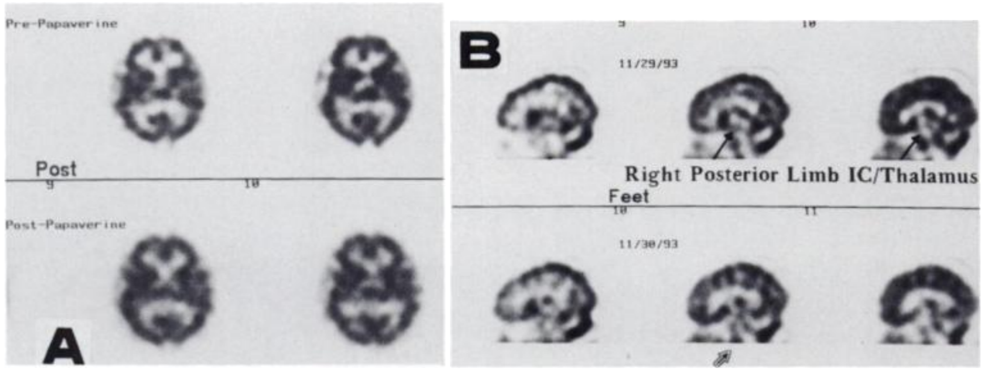

FIGURE 4. (A) Transaxial SPECT for Patient 4 before (top) and after (bottom) intra-arterial papaverine administration for treatment of vasospasm in the basilar artery. Top images reveal asymmetrically decreased perfusion in the right thalamus and posterior limb of the internal capsule which shows normalization of uptake on the bottom row after treatment. (B) Sagittal SPECT before (top) and after (bottom) intra-arterial papaverine treatment for basilar artery vasospasm. Note severe hypoperfusion in the diencephalon (denoted by the long, solid arrows) on the top and interval resolution (improved uptake) on the bottom images, best seen on the last two images (small arrow).

bers of both diseased brains and normal age-matched controls for quantitative and visual analysis.

Although the findings present on SPECT in the reported cases were simultaneously corroborated on CT in three of the four patients (yielding accurate diagnoses but perhaps not affecting treatment directly), the findings in Patient 4, which were not seen on CT, were most significant for patient management because they indicated that therapy with intra-arterial papaverine would be appropriate. Previous work by others has shown that SPECT can show cortical ischemia before conventional anatomic imaging with CT (*18*). Thus, SPECT should be particularly helpful if it is employed early enough so that the results could aid in the direction of appropriate therapy. This article suggests that high-resolution brain SPECT may also detect white matter ischemic lesions as well, adding the possibility of further subtyping the ischemic event, and describing the related diaschisis phenomenon in the cortex, a potential explanation for how some lacunes may be clinically mistaken for cortical strokes.

Nuclear medicine must provide point-of-service information to the clinicians caring for these patients if acute intervention is anticipated and based on the type of stroke imaged. Also, an attempt at providing truly complete quantitative or semiquantitative, semiautomatic ROI analysis of brain SPECT data must include sampling of the deep gray matter nuclei, seen in the study by Waldemar et al. (*5*), as well as sampling of white matter tracts instead of a simple circumferential profiling of the cortex.

CONCLUSION

In high-resolution nuclear tomographic imaging of the brain, the cortex should not be viewed exclusively. The more internal brain structures including the subcortical gray and white matter require similar attention.

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APPENDIX

The left-to-right ratio is calculated

$$\frac{L}{R} = \frac{\text{Total counts left ROI}}{\text{Total counts right ROI}}$$

for ROIs of equal size.

The side-to-side asymmetry index (SAI) is calculated after Waldemar et al. (*5*):

$$\text{SAI (\%)} = 100 \times \frac{F_i(R) - F_i(L)}{F_i(\max)},$$

where $F_i(R)$, $F_i(L)$ and $F_i(\max)$ are the mean counts per pixel in the right, left and higher of the two ROIs, respectively.

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