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Assessment of brain SPECT

Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology

A panel of experts produced this assessment paper in response to a request from the American Academy of Neurology's Therapeutics and Technology Assessment Subcommittee. The task was to evaluate the clinical utility of brain single-photon emission computed tomography (SPECT). This assessment paper is the result of a review of the current literature, the compiled comments from 13 experts to form a preliminary draft, and a subsequent final review by a panel of 12 experts. Opinions were also solicited and received from the Academy at large. This paper, provided to the Academy membership as an educational tool, will be subjected to periodic revision as new information becomes available.

Introduction to brain SPECT. SPECT was introduced in the early 1980s as an instrument for the evaluation of regional cerebral perfusion (rCP) and receptor density studies. For the performance of SPECT, a flow tracer or a receptor-binding substance is tagged with a radionuclide and injected intravenously into the patient. The radiotracer is assumed to accumulate in different areas of the brain proportionately to the rate of delivery of nutrients to that volume of brain tissue. Using a gamma camera and the techniques of CT, a three-dimensional image of the distribution of a radionuclide in the brain is obtained. Initial images, usually performed with xenon-133 (^{133}Xe), provided less than adequate anatomic resolution. This situation has been corrected in the past few years with the advent of improved cameras and radiotracers. Perfusion studies are now being used for the study of cerebrovascular disease and to aid in the differentiation of glioma from radiation necrosis, the early diagnosis of HIV encephalopathy, the study of focal epilepsy, the diagnosis of Alzheimer's disease and Huntington's chorea, and the determination of brain death.[1] Receptor-binding agents for SPECT are becoming increasingly available, although none is yet approved by the U.S. Food and Drug Administration (FDA) for clinical imaging.

One of the major reasons for the growing interest in SPECT is that it represents a less expensive functional neuroimaging technique. The older and more accurate modality for functional neuroimaging is positron emission tomography (PET). Unlike PET, SPECT cannot measure regional cerebral metabolism, but it does provide a qualitative estimate of regional cerebral blood flow (rCBF), which in many neurologic disorders is tightly coupled with brain metabolism. Thus, SPECT provides functional information not available by conventional CT or MRI at a cost similar to that of CT.

The SPECT method. SPECT images are generated using gamma cameras or ring-type imaging systems that record photons emitted by tracers trapped in the brain.[2,3] SPECT results in better image quality than two-dimensional or planar imaging because focal sources of activity are not superimposed on each other. As a result, the contrast between the target and the background (the signal-to-noise ratio) is greatly increased. Depending on the type of imaging system and tracer used, the resolution ranges from 14 to 17 mm full-width half-maximum (FWHM) for single-head gamma cameras, to 8 to 10 mm FWHM for three- and four-head camera systems, and to 7 to 8 mm FWHM for special-purpose ring-type imaging systems. In general, system cost is directly proportional to the number and complexity of camera heads or crystals. Single-head SPECT systems cost $250,000, whereas multihead cameras and ring-type systems cost between $400,000 and $1,200,000.

Scanning time in SPECT depends on the imaging system, the type of radiopharmaceutical, and the quality of image desired. High-resolution images of the whole brain can be obtained with current technology in about 20 to 30 minutes. The volume imaging capacity of most SPECT systems permits reconstruction at any angle, including the axial, coronal, and sagittal planes, or at the same angle of imaging obtained with CT or MRI to facilitate image comparisons.

A number of commercially available and experimental radiopharmaceuticals have been applied to SPECT studies of cerebral perfusion. The radiotracer is assumed to accumulate in different areas of the brain proportionally to the rate of delivery of nutrients to that volume of brain tissue and is described in ml/min per 100 g. Studies in animals and humans have demonstrated that under properly controlled conditions, SPECT data obtained with perfusion agents approximates perfusion closely enough to be meaningful in clinical and research studies.[4] Furthermore, most routine clinical applications of brain perfusion SPECT do not require quantitation of rCBF and rely exclusively on the generation of images that reflect tracer uptake and retention only. Thus, areas of abnormal activity are said to be hyper- or hypoperfused, as compared to a reference set, which is often the average cerebellar activity or the average cortical activity in the same anatomic slice.

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The FDA has approved three brain perfusion radiopharmaceutical agents for clinical use: (1) Iodine-123 (^{123}I) *N*-isopropyl-p-iodoamphetamine (IMP, Spectamine) distributes proportionately to rCBF over a wide range of flows but may be decreased with low plasma pH as in cerebral ischemia or acidosis.[5] Brain activity remains relatively constant from 20 to at least 60 minutes after injection. (2) Technetium-99m (^{99m}Tc) hexamethylpropylenamine oxime (HMPAO, Ceretec), a lipid-soluble, macrocyclic amine, is available for routine clinical use.[6] Brain uptake is rapid and reaches its maximum within 10 minutes. Radiotracer distribution remains constant for many hours after injection. The radiopharmaceutical is chemically unstable in vitro 30 minutes after preparation, but a more stable compound has been approved by the FDA. (3) ^{99m}Tc ethyl cysteinate dimer (ECD, Neurolite) has a rapid blood clearance, resulting in high brain–to–soft-tissue activity ratios early after injection, which improve with time.[7] The radiolabeled compound is stable for about 6 hours, facilitating its use for the study of episodic phenomena such as seizures. Both ^{99m}Tc HMPAO and ^{99m}Tc ECD exhibit less brain extraction than ^{123}I IMP, but the more favorable dosimetry permits a substantially higher dose (20 to 30 mCi) and a higher photon flux. Radiolabeling with ^{99m}Tc on site, followed by mandated quality-control measures such as chromatography, must be performed in a nuclear medicine laboratory by an experienced staff. These procedures are standard in all nuclear medicine services.

The inert gas ^{133}Xe has also been used to study rCBF. ^{133}Xe SPECT is performed after gas inhalation and is based on clearance techniques that relate the change in radiotracer activity over time to blood flow.[8] The principal advantage of ^{133}Xe over other tracers that remain in the brain is that the rCBF can be measured quantitatively and repeatedly without arterial sampling. ^{133}Xe does have major limitations, including poor spatial resolution and the need for specialized instrumentation.

In addition to their use in determining perfusion, radiotracers can be used to determine biochemical interactions such as receptor binding.[9] ^{123}I-labeled ligands have been developed for imaging the muscarinic, benzodiazepine, serotoninergic, and dopaminergic receptor systems. These radiotracers have not yet reached the stage of routine clinical practice.

Safety. Brain perfusion SPECT is a safe procedure. The whole body effective dose equivalent (EDE) received from the administration of ^{99m}Tc HMPAO is 0.7 rem per 20 mCi dose. This EDE value is similar to that received during a radionuclide bone scan, is 1.5 times that received from a CT scan of the abdomen and pelvis, and is 43% of the average annual background radiation in the United States. Patients must remain still during the course of the study, which usually lasts 20 to 30 minutes. Most state-of-the-art imaging systems are designed to reduce head motion and patient discomfort. Most clinical applications do not require arterial sampling.

SPECT in brain disorders. The interest in SPECT has spawned an abundance of published reports over the past few years. Unfortunately, many of the reports comprise only a few patients, and large, well-controlled studies are few. In addition, most studies have used as a standard the clinical diagnosis, lacking pathologic confirmation. Another caveat has to do with the variable quality of the techniques used for clinical SPECT, which is more dependent on the operator than are CT or MRI. The reported results have usually been obtained at well-established nuclear medicine services and may not be generalizable to all institutions. Given the complexity of the information derived from functional neuroimaging, the interpretation of results often requires a close collaboration between nuclear medicine physicians and clinicians.

Stroke. SPECT is a sensitive indicator of perfusion; it supplements the anatomic information from CT and MRI in the evaluation of cerebrovascular disease. Abnormal patterns of blood flow are recognized either as areas of hypoactivity (focal or diffuse) or hyperactivity (hyperemia or luxury perfusion).[10]

Acute stroke. CT and MRI scans provide information only on anatomic changes, and for this reason, remain normal for some time after the onset of symptoms. Eight hours after an infarction, approximately 20% of CT scans will be positive;[11,12] nearly 90% of SPECT scans will be.[10,12-15] Several hours must pass before changes can be detected by conventional MRI. False-negative rates of 7% to 20% have been reported for acute stroke, depending on the size of infarction and the strength of the magnet.[16] Two large, prospective, blinded studies examined the ability of brain SPECT to localize ischemic stroke. Sensitivities of 61% to 74% (about 85% for nonlacunar strokes) and specificities of 88% to 98% were reported.[17]

Prognosis/recovery from stroke. Anatomic imaging has limited prognostic capability.[18] A potential advantage of functional imaging such as SPECT is that demonstration of "activation" by tasks challenging neurologic deficits may have prognostic value.[19] SPECT perfusion changes correlate with the clinical examination at the time of the study;[20-22] however, attempts to correlate acute SPECT lesion size with outcome have had mixed results, perhaps because in various studies SPECT was performed at different times within the first week after stroke. In a study of very early SPECT (<6 hr after stroke), early severe decreases in CBF were highly predictive (92%) of poor neurologic outcome.[23] Other studies have shown a good correlation, especially when the three-dimensional volume of the defect is used.[24] Based on several clinical studies, SPECT should be considered an investigational tool for the assessment of prognosis after stroke.

Stroke subtypes. The limitations and difficulties in classifying stroke subtypes on clinical grounds and anatomic imaging (angiography, CT scan) are well described.[25] Consideration of stroke subtype is important for treatment, recurrence, recovery, and mortality.[26-28] For instance, patients with cortical stroke are more likely to need anticoagulation than those with lacunar stroke. The need to rapidly and accurately differentiate stroke subtypes is becoming increasingly important as more specific stroke therapies are being evaluated. Although the hemodynamic status, as determined by PET in patients with greater than 75% carotid stenosis, did not predict stroke recurrence after 1 year,[29] the ability to identify patients with low flow states due to asymptomatic carotid disease might permit appropriate selection of cases for endarterectomy. Similarly, demonstration of hemodynamically significant carotid stenosis in the setting of an acute infarct may prompt the use of revascularization as opposed to anticoag-

ulation or thrombolytic therapy. Patterns for distal field infarction, similar to those described for CT and MRI, can be seen earlier after stroke on SPECT scans.[10,30,31] Similarly, a wedge-shaped defect is often seen with embolic infarction. A normal SPECT with a lacunar syndrome may be strongly predictive of small vessel disease.[10] In a study of 106 patients with hemispheric stroke (lacunar in 28), a negative SPECT was considered to imply lacunar disease. Using this premise, SPECT was 68% sensitive and 100% specific for lacunar stroke.[32] Based on several clinical studies, SPECT should be considered a promising tool for the determination of stroke type.

Data from several well-designed clinical studies indicate that the detection of acute ischemia is an established application of SPECT. Although not a frequent occurrence, neurologic deficits associated with seizures may mimic stroke. As discussed below, SPECT in the ictal phase of a focal seizure shows increased perfusion, facilitating the differentiation of these disorders from ischemic stroke. In ischemic stroke, SPECT is helpful to differentiate lacunar from cortical disease early in the course of the disorder, when CT and MRI may still be normal. Decreased cortical perfusion is more likely to be related to embolic disease that may require a cardiac workup and anticoagulation.

Transient ischemic attacks. The efficacy of SPECT in the evaluation of transient ischemic attacks (TIAs) is highly time dependent. Studies of CBF suggest that up to 60% of patients with TIAs will have abnormalities if examined on the day of admission, 40% by the second day,[33] and the number continues to fall during the first week after the event.[10] The sensitivity of SPECT imaging in TIAs can be improved with the addition of reactivity testing with acetazolamide, which may also provide information on the mechanism of ischemia.[34] SPECT may be useful in identifying patients at especially high risk for early stroke following a TIA. A persistent reduction in CBF of greater than 30% in the days after a TIA may be associated with a high risk of subsequent infarction in the first week after the TIA.[35] Although still at an investigational stage, the diagnosis and prognosis of TIA may become one of the most helpful applications of SPECT.

Subarachnoid hemorrhage. Regional hypoperfusion seen on SPECT correlates with the presence and severity of delayed neurologic deficits.[36] SPECT facilitates the early diagnosis of cerebral hypoperfusion due to vasospasm and may help in differentiating hypoperfusion from other causes of deterioration after subarachnoid hemorrhage (SAH). SPECT has been used to evaluate steal in arteriovenous malformations. The presence of severe steal has prompted staging of the surgical resection and encouraged embolization as a preliminary treatment.[37] Based on several well-controlled clinical studies, detection of ischemia due to vasospasm after SAH seems a promising application for SPECT.

Neoplasms. Tracers labeled with thallium-201 (^{201}Tl) have been used to quantitate the malignancy grades of gliomas and to differentiate radiation necrosis from tumor recurrence. Higher malignancy tumors have a greater radionuclide uptake.[38] Dual-isotope SPECT with ^{201}Tl to label the tumor and ^{99m}Tc HMPAO to evaluate perfusion correlated with the pathology in 14 of 15 cases.[39] The results of this clinical study suggests that the role of SPECT in differentiating between radiation necrosis and recurrent tumor should continue to be investigated.

AIDS encephalopathy. SPECT in HIV encephalopathy shows decreased cortical uptake, with or without focal defects, multifocal defects in the central gray nuclei, and decreased uptake in the white matter of the hemispheres.[40] In a controlled study, 94% of the SPECT scans of 32 HIV-positive individuals were correctly classified.[41] SPECT is particularly useful in instances of psychosis or mild attentional impairment or depression in HIV-positive individuals with a normal CT or MRI.[40] The characteristic pattern described above would favor HIV encephalopathy rather than reactive psychosis or depression. Based on several well-designed clinical studies, the early diagnosis of HIV encephalopathy seems a promising application of SPECT.

Head trauma. Early SPECT reveals more extensive perfusion abnormalities than anatomic changes seen on CT early after trauma.[42-44] The extent of these changes seem to correlate with the clinical severity of post-traumatic syndrome.[45,46] In a controlled study, 11 of 14 patients with normal CT scans had abnormal SPECT scans in the 48 hours after mild head injury.[47] In minor to severe head injury, SPECT performed several months after injury was more sensitive in showing abnormalities than CT (66% to 80% versus 53% to 34%) or MRI (45%), but the clinical significance of these changes is uncertain.[45,48] The scientific literature does not now support the routine use of SPECT for the evaluation of patients with closed head injury or postconcussion syndrome. Based on several small clinical studies, SPECT should continue to be used as an investigational tool for the study of mild head trauma.

Seizures. Seizures are associated with dramatic increases in cerebral blood flow, localized in partial seizures and global during generalized seizures, as reflected on perfusion SPECT.[49] Other imaging modalities help in localizing abnormal epileptogenic tissue. Quantitative MRI has a sensitivity of 80% to 90% for the lateralization of temporal lobe epilepsy[50] and is also helpful in the detection of cortical abnormalities in children with intractable epilepsy.[51] However, there are instances where ictal SPECT has identified lesions not detected by MRI.[52] Depth electrocorticography and intraoperative electrocorticography, though accurate in many forms of epilepsy, are both highly invasive. In cortical developmental disorders, these EEG techniques often fail to localize the epileptogenic area.[53] SPECT imaging may offer a safe and accurate alternative.[52,54]

A SPECT study showing increased rCP ictally in the same region that shows decreased rCP interictally provides strong evidence for the epileptogenic nature of the lesion.[55,56] In complex partial seizures, the seizure focus has been identified in 71% to 93% of ictal SPECT studies with a positive predictive value of 95%, and interictally, SPECT has a sensitivity of 40% to 58% with positive predictive values of 80% to 87%.[55,57-63] EEG findings and rCP can be compared with the use of SPECT. With ^{99m}Tc agents, a SPECT scan taken several hours after the injection will reflect blood flow at the time of injection.[57] Thus, the tracer can be injected in the EEG laboratory and then the patient is transported to Nuclear Medicine for SPECT. SPECT has been used to clarify the diagnosis and locate the focus in epilepsia partialis continua with a negative EEG.[64] In secondarily generalized epilepsy, SPECT may show increased CBF locally despite a clinical picture sug-

Table *Summary of the effectiveness of SPECT for brain applications*

Application	Rating	Quality of evidence	Strength of evidence
Stroke			
Detection of acute ischemia	Established	Class II	Type B
Determination of stroke subtypes	Promising	Class II	Type C
Vasospasm following SAH	Promising	Class II	Type B
Prognosis/recovery from stroke	Investigational	Class II	Type C
Monitoring therapies	Investigational	Class III	Type C
Diagnosis of TIA	Investigational	Class III	Type C
Prognosis of TIA	Investigational	Class II	Type C
Neoplasm			
Grading of gliomas	Investigational	Class III	Type C
Differentiating radiation necrosis from tumor recurrence	Investigational	Class II	Type B
HIV encephalopathy	Investigational	Class II	Type B
Head trauma	Investigational	Class II	Type C
Epilepsy			
Presurgical ictal detection of seizure focus	Established	Class II	Type B
Localization of seizure focus	Promising	Class II	Type C
Differential diagnosis of ictus	Investigational	Class III	Type C
Interictal detection of seizure focus	Investigational	Class III	Type C
Determination of seizure subtypes	Investigational	Class III	Type C
Receptor studies	Investigational	Class III	Type C
Monitoring therapy	Doubtful	Class III	Type D
Alzheimer's disease			
To support clinical diagnosis	Established	Class II	Type B
Huntington's chorea	Investigational	Class III	Type C
Persistent vegetative state	Investigational	Class III	Type C
Brain death	Promising	Class III	Type C

SAH = subarachnoid hemorrhage; TIA = transient ischemic attack; HIV = human immunodeficiency virus.

gesting a nonfocal onset.[55,65] SPECT changes may also be useful in differentiating an epileptic disorder from a psychogenic one (pseudoseizure).[57]

Based on several clinical studies, SPECT is an established technique for the presurgical localization of seizure foci if performed during the ictal phase. Studies straddling the ictal and postictal phases may be misleading. Ictal studies are being facilitated by the availability of more stable radiopharmaceuticals.

Other applications are at an investigational stage. SPECT has been used to map the area perfused with barbiturate during the Wada test in the course of the evaluation for temporal lobe epilepsy surgery.[66] The accuracy of SPECT localization of a seizure focus can be expected to improve further with the use of new radiopharmaceuticals directed at specific neurotransmitter or antiepileptic medication binding sites.[67,68]

Alzheimer's disease. In Alzheimer's disease (AD), SPECT shows decreased perfusion in the association cortex of the parietal lobe and the posterior temporal regions. Frontal association cortex is predominantly affected in some cases, but usually it is not involved until late in the course of the disease. The occipital lobes are less involved and the paracentral cortex is spared.[69-73] Although SPECT studies have been reported in more than 500 patients with AD, in most cases the diagnosis was made clinically, and only in 53 patients was it confirmed by autopsy.[74-78] Controlled studies of SPECT in AD have shown the sensitivity of this procedure to vary from 50% to 95%.[69,70,79] The best results have been reported in the more recent studies using higher resolution equipment.[70,80] In small studies there has been no overlap between patients and controls, but this is probably an artifact of sample size.[81] SPECT is more often abnormal in severely affected individuals.[70,82] However, even in mild AD (Mini-Mental State Examination[83] score from 20 to 24, Blessed Dementia Scale[84] $\leq$10), 80% of the patients have abnormal SPECT studies.[72,85,86] Still, neuropsychological abnormalities precede SPECT changes in some cases.[85] The pattern of parietotemporal hypoperfusion is not specific for AD. Similar patterns have been reported in other disorders, including parkinsonism with dementia[87-89] and mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS).[90]

Although a controlled study that directly compares perfusion SPECT in patients with AD to the pseudodementia of depression is lacking, the SPECT patterns of the two

entities differ enough to suggest that the clinician may find SPECT useful to differentiate them. In depression, SPECT may be normal or show diffuse or frontal hypoperfusion. A patient with mild memory loss who otherwise has a normal workup, but whose SPECT shows the characteristic AD pattern, is more likely to have AD than one whose SPECT is normal. In selected cases, this information may be important in planning for the care of the patient. Based on several well-designed clinical studies and several clinicopathologic series, SPECT can be considered an established technique to support the clinical diagnosis of AD.

Receptor and activation studies may improve the sensitivity and specificity of SPECT for AD. The regional density of muscarinic receptors in dementia has been measured using ^{123}I-labeled 3-quinuclidinyl-4-idobenzilate (^{123}I QNB).[91] Eight of 12 patients with AD had focal cortical defects in either frontal or posterior temporal cortex. Patients with Pick's disease had prefrontal and anterior temporal uptake below the control range. Acetazolamide causes an increase of cerebral perfusion owing to vasodilation in areas of the brain with an intact vascular reserve, but not where the arterioles are already fully dilated, such as ischemic areas. After the intravenous administration of 1 g of acetazolamide, perfusion increased in the originally hypoperfused parietotemporal areas of patients with AD, whereas it remained the same or decreased in patients with cerebrovascular disease.[92] Central cholinergic stimulation with physostigmine produced a focal increase in perfusion in the posterior parietotemporal region in patients with AD but not in controls.[93] To date, the number of patients studied with these techniques is small and therefore the clinical utility of the techniques remains unclear.

Huntington's chorea. On SPECT, the caudate nuclei appear hypoperfused, even in the early stages, when there is no structural evidence of caudate atrophy on CT or MRI.[87,89,94,95] This finding is particularly useful in patients with questionable clinical findings such as very mild rigidity or chorea. Because large clinical studies are not available and genetic studies may soon prove more specific and accessible, SPECT is an investigational technique for the early diagnosis of Huntington's chorea.

Persistent vegetative state. In a study of 12 patients with persistent vegetative state admitted consecutively for early rehabilitation after head injury, a global reduction of cortical blood flow on SPECT was a reliable predictor of poor long-term outcome (3-year follow-up), but the demonstration of only focal deficits did not reliably indicate a favorable outcome.[96] SPECT is a useful investigational tool for the study of the persistent vegetative state.

Diagnosis of death on neurologic criteria. Cerebral perfusion imaging with SPECT agents, particularly ^{99m}Tc compounds, is superior to the conventional radionuclides used for the diagnosis of brain death.[97] Absent cerebral activity is clearly shown on SPECT, but tomography is generally not needed; the anterior and two lateral planar views are sufficient.[97] This technique has not been compared to conventional angiography but seems promising for the diagnosis of death based on neurologic criteria.

Summary. Brain SPECT is beginning to emerge as a helpful tool in the evaluation of a variety of neurologic disorders (table). Studies are needed to further define the cost-effectiveness of this modality.

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DEFINITIONS

Safety. A judgment of the acceptability of risk in a specified situation, e.g., for a given medical problem, by a provider with specified training, at a specified type of facility.

Effectiveness. Producing a desired effect under conditions of actual use.

Established. Accepted as appropriate by the practicing medical community for the given indication in the specified patient population.

Promising. Given current knowledge, this technology appears to be appropriate for the given indication in the specified patient population. As more experience and long-term follow-up are accumulated, this interim rating will change.

Investigational. Evidence insufficient to determine appropriateness; warrants further study. Use of this technology for given indication in the specified patient population should be confined largely to research protocols.

Doubtful. Given current knowledge, this technology appears to be inappropriate for the given indication in the specified patient population. As more experience and long-term follow-up are accumulated, this interim rating will change.

Unacceptable. Regarded by the practicing medical community as inappropriate for the given indication in the specified patient population.

Quality of Evidence Ratings

Class I. Evidence provided by one or more well-designed, randomized, controlled clinical trial.

Class II. Evidence provided by one or more well-designed clinical studies, e.g., case control, cohort studies.

Class III. Evidence provided by expert opinion, nonrandomized historic controls, or case reports of one or more.

Suggested Strength of Recommendations Ratings

Type A. Strong positive recommendation, based on Class I evidence or overwhelming Class II evidence when circumstances preclude randomized clinical trials.

Type B. Positive recommendation, based on Class II evidence.

Type C. Positive recommendation, based on strong consensus of Class III evidence.

Type D. Negative recommendation, based on inconclusive or conflicting Class II evidence.

Type E. Negative recommendation, based on evidence of ineffectiveness or lack of efficacy, based on Class II or Class I evidence.

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