10. Baxter LR, Schwartz JM, Phelps ME, et al. Reduction of prefrontal cortex glucose metabolism common to three types of depression. *Arch Gen Psychiatry* 1989;46:243–250.
11. Mayberg HS, Lewis PJ, Regenold W, Wagner HN. Paralimbic hypoperfusion in unipolar depression. *J Nucl Med* 1994;35:929–934.
12. Baxter LR Jr, Schwartz JM, Mazziotta JC, et al. Cerebral glucose metabolic rates in nondepressed patients with obsessive-compulsive disorder. *Am J Psychiatry* 1988;145:1560–1563.
13. Rauch SL, Jenike MA, Alpert NM, et al. Regional cerebral blood flow measured during symptom provocation in obsessive-compulsive disorder using oxygen-15-labeled carbon dioxide and positron emission tomography. *Arch Gen Psychiatry* 1994;51:62–70.
14. Reiman EM, Raichle ME, Butler FK, et al. A focal brain abnormality in panic disorder: a severe form of anxiety. *Nature* 1984;310:683–685.
15. Gur RE, Resnick SM, Gur RC. Laterality and frontality of cerebral blood flow and metabolism in schizophrenia: relationship to symptom specificity. *Psychiatry Res* 1989;27:325–334.
16. Buchsbaum MS. The frontal lobes, basal ganglia and temporal lobes as sites for schizophrenia. *Schizophrenia Bull* 1990;16:379–391.
17. Zametkin AJ, Nordahl TE, Gross M, et al. Cerebral glucose metabolism in adults with hyperactivity of childhood onset. *N Engl J Med* 1990;323:1361–1366.
18. Volkow ND, Hitzemann R, Wang GJ, Wolf AP, Dewey SJ. Decreased brain metabolism in neurologically intact healthy alcoholics. *Am J Psychiatry* 1992;149:1016–1022.
19. Volkow ND, Fowler JS, Wolf AP, Hitzemann R, et al. Changes in brain glucose metabolism in cocaine dependence and withdrawl. *Am J Psychiatry* 1991;148:621–626.
20. Holman BL, Garada B, Johnson KA, Mendelson J, et al. Comparison of brain perfusion SPECT in cocaine abuse and AIDS dementia complex. *J Nucl Med* 1992;33:1312–1315.
21. Ichise M, Salit IE, Abbey SE, et al. Assessment of regional cerebral perfusion by ^{99m}Tc HMPAO SPECT in chronic fatigue syndrome. *Nucl Med Commun* 1992;13:767–772.
22. Goldstein JA, Mena I, Jouanne E, Lesser I. The assessment of vascular abnormalities in late life chronic fatigue syndrome by brain SPECT: comparison with late life major depressive disorder. *J Chronic Fatigue Syndrome* 1995;1:55–79.
23. Schwartz RB, Komaroff AL, Garada BM, et al. SPECT imaging of the brain: comparison of findings in patients with chronic fatigue syndrome, AIDS dementia complex and major unipolar depression. *AJR* 1994;162:943–951.
24. Callender TJ, Morrow L, Subramanian K, Duhon D, Ristovv M. Three dimensional brain metabolic imaging in patients with toxic encephalopathy. *Environmental Res* 1993;60:295–319.
25. Heuser G, Mena I, Alamos F. NeuroSPECT findings in patients exposed to neurotoxic chemicals. *Toxicol Industrial Health* 1994;10:561–571.
26. Simon TR, Hickey DC, Fincher CE, Johnson AR, Ross GH, Rea WJ. Single-photon emission computed tomography of the brain in patients with chemical sensitivities. *Toxicol Industrial Health* 1994;10:573–577.
27. Volkow ND, Tancredi L. Neural substates of violent behavior: a preliminary study with PET. *Br J Psychiatry* 1987;151:668–673.
28. Volkow ND, Tancredi LR, Grant C, et al. Brain glucose metabolism in violent psychiatric patients: a preliminary study. *Psychiatry Res Neuroimaging* 1995;61:243–253.
29. Raine A, Buchsbaum MS, Stanley J, et al. Selective reductions in prefrontal glucose metabolism in murderers. *Biol Psychiatry* 1994;36:365–373.
30. Mayberg HS. Critique: SPECT studies of multiple chemical sensitivity. *Toxicol Industrial Health* 1994;10:661–666.
31. Mayberg HS. Functional brain scans as evidence in criminal court: an argument for caution. *J Nucl Med* 1992;33:18N–25N.
32. Metter EJ, Kempler D, Jackson CA, et al. Cerebral glucose metabolism in Wernicke's, Brocas's and conduction aphasia. *Arch Neurol* 1989;46:27–34.
33. Pappata S, Mazoyer B, Tran Dinh S, et al. Effects of capsular or thalamic stroke on metabolism in the cortex and cerebellum: a PET study. *Stroke* 1990;21:519–524.
34. Jagust WJ, Reed Br, Seab JP, et al. Clinical-physiological correlates of Alzheimer's disease and frontal lobe dementia. *Am J Physiol Imaging* 1989;4:89–96.
35. Fazio F, Perani D, Gilardi MC, et al. Metabolic impairment in human amnesia: a PET study of memory networks. *J Cereb Blood Flow Metab* 1992;12:353–358.
36. Haxby JV, Duara R, Grady CL, Cutler NR, Rapoport SI. Relations between neuropsych and cerebral metabolic asymmetries in early Alzheimer's disease. *J Cereb Blood Flow Metab* 1985;5:193–200.
37. Grafton ST, Mazziotta JC, Pahl JJ, et al. A comparison of neurological, metabolic, structural and genetic evaluations in persons at risk for Huntington's disease. *Ann Neurol* 1990;28:614–621.
38. Fletcher JW, Woolf SH, Royal HD. Consensus development for producing diagnostic procedure guidelines: SPECT brain perfusion imaging with exametazime. *J Nucl Med* 1994;35:2003–2010.
39. Weber DA, Devous MD, Tikofsky RS. Brain SPECT perfusion imaging: image acquisition, processing, display and interpretation. In: Springfield, VA: National Technical Information Service, 1991; *Proceedings of Workshop Held at Brookhaven National Laboratory*, October 8–9, 1991.
40. Loessner A, Alavi A, Lewandrowski KU, Mozley D, Souder E, Gur RE. Regional cerebral function determined by FDG-PET in healthy volunteers: normal patterns and changes with age. *J Nucl Med* 1995;36:1141–1149.
41. Thornton JI. Courts of law versus courts of science: a forensic scientist's reaction to Daubert. *Shepard's Expert and Scientific Evidence Quarterly* 1994;1:475–486.
42. U.S. Supreme Court. Frye versus United States. 1923;293 F. 1013, 1014.
43. U.S. Supreme Court. Daubert versus Merrell Dow Pharmaceuticals. *113 Supreme Court*. 1993:2786.

Brain SPECT and Thrombolysis in Acute Ischemic Stroke: Time for a Clinical Trial

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Key Words: brain SPECT; acute stroke; thrombolysis

J Nucl Med 1996; 37:1259–1262

THROMBOLYSIS FOR STROKE

The spirit of resignation in management of patients with acute stroke will likely disappear when measures for brain tissue rescue are proven effective (*1*). The first four randomized placebo-controlled trials showed no benefit from intravenous thrombolysis with streptokinase (SK) and tissue plasminogen activator (tPA) (*2*). This was due to excessive numbers of hemorrhagic transformations (HT) of brain infarction and deaths in the treatment group which exceeded 30% of treated patients in the European and Australian trials (*2*). The only trial so far to demonstrate the therapeutic effect of tPA was the National Institutes of Health-sponsored study in which half of the patients were treated within 90 min of stroke onset (*3*). Yet the incidence of symptomatic HT was at least ten times greater with tPA than in the placebo group: 6.4% versus 0.6% (*3*).

The entry criteria in the thrombolytic trials include: the duration of symptoms, clinimetric assessment of stroke severity and admission CT scan. These tests are inadequate to determine stroke pathogenesis and depth of ischemia, and thus large numbers of patients are required to demonstrate the benefit from treatment, if any, compared to a placebo group (*2,3*). A natural extension of first successful trials would be to determine a time threshold when thrombolytic agents become more harmful than useful, and a target group of patients for safe

Received Apr. 1, 1996; revision accepted Apr. 2, 1996.

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thrombolytic treatment (*2,3*). For this purpose, it was suggested that noninvasive brain perfusion studies may prove useful adjuncts to clinical examination and CT-scanning, and future trials should include some form of vascular imaging (*2,4*).

BRAIN SPECT METHODS

SPECT helps to determine the presence of collateral flow, depth of ischemia and stroke pathogenesis during the "therapeutic window" when CT scans usually fail to show an ischemic lesion (*4,5*). The role of SPECT in acute stroke setting is still emerging (*4,5*) because no treatment decisions are made based on SPECT findings. Furthermore, SPECT does not influence clinical decision-making directly because no randomized multicenter trials were performed utilizing SPECT to select patients for treatment. The technology has, however, evolved to allow fast and informative evaluation of acute stroke patients.

Selection of methods and tracers for brain SPECT in acute stroke setting is influenced by several specific considerations. Most modern brain dedicated SPECT systems aim at providing multiple cross-sectional images covering the whole brain with spatial resolution of 7–10 mm. This resolution is achieved by using a fairly long data acquisition time, typically in the order of 30 min or longer. This is an extremely long time if one wants to perform acute studies within the first few hours for selecting stroke patients for active treatment. A cruder approach can be used in emergency situations whereby only 2–4 transaxial slices are recorded and with a spatial resolution of about 12 mm. Blood flow recordings by ^{133}Xe or ^{99m}Tc-labeled tracers (*6*) are made within a few minutes. Technetium-99m-hexametyl-propylene-amine-oxime (HMPAO) is trapped by a simple chemical interaction with intracellular glutathione (*7*) which levels increase with reperfusion (*8*). This leads to an increased retention, or hyperfixation (*9*) seen in some patients during the subacute phase. Technetium-99m-ethylendiol-cysteine-diethylester (ECD) retention is dependent on brain esterase activity. Thus, only hypofixation of ECD is usually seen during the subacute phase with no reflow phenomenon visualized beyond the first 24 hr (*6*).

If urgency of starting thrombolytic therapy precludes immediate scanning then the excellent retention of the ^{99m}Tc compounds allows one to simply inject the tracer acutely but delay the scanning for up to 8 hr: the delayed image is a "frozen snap-shot" of the brain perfusion at the time of injection (*7,9*).

To date, no other technique has been developed that allow estimates of collateral blood flow. The so-called "cold" xenon enhanced x-ray-CT scanning technique is not suited for acutely ill and often restless patients; PET scanning is logistically difficult and magnetic resonance imaging has not been able so far to measure brain perfusion quantitatively. We believe that acute SPECT can reliably evaluate cerebral ischemia and has potential to better select candidates for thrombolytic therapy. In particular, SPECT imaging in the first few hours after stroke onset can provide information about the intensity and extent of ischemia, as well as the degree of collateral flow. A plea is made, therefore, for wider use of acute SPECT studies in cerebral ischemia as all evidence points to the key importance of not only considering duration of ischemia but also its intensity when thrombolysis is considered (*2,3,4*).

REPERFUSION AND NON-NUTRITIONAL FLOW

Rapid reperfusion of the ischemic penumbra may salvage viable neurons (*10*). The Australian Streptokinase Trial (ASK) has recently concluded, demonstrating no overall benefits for patients treated with intravenous streptokinase (SK) within 4 hr of acute ischemic stroke (*11*). Patients entered after 3 hr had an increased mortality with thrombolysis, linked in part to hemorrhagic transformation. Conversely, patients treated within 3 hr (an a priori hypothesis) had no excess of death and significantly improved outcomes in the SK group. The relationship between SPECT-measured acute reperfusion and clinical gains, however, is controversial. Some authors have correlated acute reperfusion with neurological or functional improvement (*12,13*), but others have found little or no relationship (*14,15*). The discrepancies between the results of these studies could well be explained by the confounding problem of non-nutritional flow, or "luxury" perfusion syndrome (*16*). Non-nutritional flow can be diagnosed by SPECT retrospectively, as the degree of acute reperfusion that is not maintained at the outcome stage of chronic brain infarction, expressed as hypoperfusion volumes. Reperfusion should be measured early after therapy, because the hyperfixation of HMPAO and hypofixation of ECD do not reflect actual brain perfusion in the subacute phase (*6,9*).

The ASK trial was the first to use SPECT as an add-on test to evaluate brain perfusion before and after administration of SK or placebo (*12*). In this trial, SK administration was associated with a trend to greater acute reperfusion compared with placebo, using SPECT, performed before treatment and 24 hr later. However, a paradoxical increase in hypoperfusion volume between the acute and outcome studies at 3 mo was found despite neurological and functional improvement in the SK-treated patients (*17,18*). This finding could be best explained by the presence of early non-nutritional flow or luxury reperfusion through nonviable brain tissue (*18*). In this study (*18*), non-nutritional flow predicted a worse functional outcome after 3 mo and was also linked to hemorrhagic transformation. This suggests that streptokinase increases luxury perfusion after stroke, which might potentiate reperfusion injury. SPECT measurement of the varying components of nutritional and non-nutritional reperfusion after stroke requires outcome measurements as well as analysis of acute reperfusion.

Finally, acute measurements of crossed cerebellar diaschisis, which correlate with metabolic depression and infarct size, might be a prospective indication of non-nutritional flow with HMPAO-SPECT (*19*). These measurements on SPECT may prove useful in selecting individuals with maximum therapeutic response for tissue rescue.

STROKE PATHOGENESIS AND OUTCOME

SPECT provides information on stroke pathogenesis and outcome, which is relevant for clinical decision-making (*4*). In the natural history studies, an association was found between SPECT perfusion patterns and pathogenetic mechanisms of ischemia (*20–23*). First, focal absence of perfusion was seen in patients with ischemic strokes due to occlusion of a major artery. Second, patients with lacunar stroke often presented with normal SPECT study, and finally, increased uptake of HMPAO was associated with suspected cardioembolism (*20–23*). This advantage of SPECT could help to avoid inaccuracies in early classification of patients by stroke pathogenic mechanisms bound to clinical trials based on clinical and CT examinations alone. For example, despite randomization in the NIH-rt-PA study, more patients in the tPA group had small-vessel occlusive disease compared to placebo group at baseline clinical examination (51/253 versus 30/272, $p = 0.018$) (*3*). Furthermore, the percent of patients with a more favorable outcome was the highest in this group compared to large-vessel occlusive or cardioembolic strokes (75% versus 49% and 46%, respectively) (*3*). One explanation could be that tPA "saves" the cortex in large-vessel occlusive or cardioembolic stroke and

limits the deficit to pure motor or sensory symptoms producing artificial increase in the number of patients small-vessel disease benefiting from thrombolysis. This question would have been answered if baseline SPECT would have been obtained in these patients.

From a prognostic viewpoint, SPECT predicted improvement following stroke with accuracy similar to the Canadian Neurological Scale (*24*) in the natural history studies (*20,22,23*). The initial perfusion defect on SPECT also correlated with stroke severity and outcome assessed by the NIH Stroke Scale and Barthel Index (*15*) showing feasibility of SPECT for selecting or stratifying patients in clinical trials during the first hours of stroke. Moreover, SPECT have been used in a randomized trial performed at a single center to assess the effect of antihypertensive medication on brain perfusion in acute stroke (*25*).

INTERPRETING SPECT SCANS

Quantitation of brain SPECT data can be accomplished using the region-of-interest methods as suggested by Mountz which modifications were used in a variety of studies (*4,15,17*). These methods, however, are relatively time-consuming and may not be suitable for triage of acute stroke patients. To save time during triage, HMPAO-SPECT may also be interpreted semiquantitatively using a simple visual image analysis. Five distinct patterns of brain perfusion were reported (normal, high, mixed, low and absent) with good intra- and interobserver reproducibility (*26*). In this study, the nuclear medicine physicians and the neurologists interpreted SPECT with similar accuracy (kappa > 0.8) (*26*). As interpreted by visual pattern recognition during the first 6–48 hr, SPECT predicted outcome better than clinical examination due to distinction between the focal absence of perfusion and presence of collateral flow (*3,25,26*). Furthermore, SPECT helps to identify patients with minor strokes since normal brain perfusion during the first hours after the stroke is a favorable prognostic sign (*26*). Therefore, visual analysis of brain SPECT images may prove useful particularly in the emergency situations.

HMPAO and Stroke Outcome

Asymmetry of HMPAO distribution during the first 48 hr predicts stroke outcome with accuracy similar or superior to clinical scales (*4,26,27*). The focal absence of HMPAO uptake implies failure of collateral flow distal to obstruction and poor prognosis, thus suggesting dismal likelihood of benefit from acute treatment (*15,20,25,26*). Unlike the focal absence, acutely decreased HMPAO uptake indicates some collateral flow and better chances of recovery comprising patients who may be a target group for therapeutic interventions (*25,26*). Increased uptake of HMPAO or hyperfixation is relatively common after reperfusion and is often regarded as an artifact (*9*), yet it is associated with improved outcome (*22,25,28*). Since intracellular glutathione protects against free radicals (*29*) its level increases during reperfusion (*8*). Thus, HMPAO uptake reflects a level of endogenous neuroprotection. Normal HMPAO uptake during the first hours of ischemia identifies patients with reversible deficits, despite the severity of dysfunction on admission (*15,20,26*). The prognostic value of HMPAO-SPECT scans was studied the most in the natural history studies in acute stroke setting (*4*). HMPAO-SPECT is feasible for acute interventional trials, in which the hypotheses outlined above can be tested. The value of other tracers need to be evaluated in separate trials since different trapping mechanisms and imaging properties will likely produce different diagnostic criteria.

CONCLUSION

SPECT has an advantage of noninvasive evaluation of brain perfusion and it demonstrates brain collateral flow, depth of ischemia, lesion volume and metabolism. Readily available from acute SPECT studies, this information may prove invaluable to determine a target group of patients for selective interventions. The clinical value of SPECT would be established if this promising method is included in future trials of acute treatment for stroke. Now is the time when clinical demands meet the promises of SPECT technology, and the opportunity exists to establish SPECT as a diagnostic test for stroke. Despite technological improvements in SPECT scanning, its clinical utilization will largely depend on its usefulness and cost-effectiveness (*30*), parameters which can only be established through randomized multicenter studies. Integrating SPECT into an interventional clinical trial may require certain changes in nuclear medicine, but this is a goal worthwhile to explore.

ACKNOWLEDGMENT

Presented in part at the Satellite Symposium, "Brain SPECT: Implications for Therapy," sponsored by Amersham Healthcare Intl., October 18, 1995, Prague, Czech Republic.

REFERENCES

1. Adams HP, Brott TG, Crowell RM, et al. Guidelines for the management of patients with acute stroke. *Stroke* 1994;25:1901–1914.
2. Fischer M, Pessin MS, Furlan AJ. ECASS: lessons for future thrombolytic stroke trials. *JAMA* 1995;274:1058–1059.
3. The National Institutes of Neurological Disorders and Stroke rt-PA Stroke Study Group. Tissue plasminogen activator for acute ischemic stroke. *N Engl J Med* 1995;333:1588–1593.
4. Masdeu JC, Brass LM, Holman BL, Kushner MJ. Brain single-photon emission computed tomography. *Neurology* 1994;44:1970–1977.
5. Holman LB, Devous MD. Functional brain SPECT: the emergence of a powerful method. *J Nucl Med* 1992;33:1888–1904.
6. Morgan GF, Costa DC. Radiopharmaceuticals for conventional blood-brain barrier and brain perfusion studies. In: Costa DC, Morgan GF, Lassen NA, eds. *New trends in nuclear neurology and pscychiatry.* London: John Libbey and Co. Ltd.; 1993;65–84.
7. Neirinckx RD, Burke JF, Harrison RC, Forster AM, Andersen AR, Lassen NA. The retention mechanism of technetium-99m-HMPAO: intracellular reaction with glutathione. *J Cereb Blood Flow Metab* 1988;8:S4–S12.
8. Simonson AG, Zhang J, Canada AT, Su YF, Benveniste H, Piantadosi CA. Hydrogen peroxide production by monoamine oxidase during ischemia-reperfusion in the rat brain. *J Cereb Blood Flow Metab* 1993;13:125–134.
9. Sperling B, Lassen NA. Hyperfixation of HMPAO in subacute ischemic stroke leading to spuriously high estimates of cerebral blood flow by SPECT. *Stroke* 1993;24:193–194.
10. Haley EC, Brott TG, Sheppard GL, et al. Pilot randomized trial of tissue plasminogen activator in acute ischemic stroke. *Stroke* 1993;24:1000–1004.
11. Donnan GA, Davis SM, Chambers BR, et al. Trials of streptokinase in severe acute ischemic stroke [Letter]. *Lancet* 1995;345:578–579.
12. Baird AE, Donnan GA, Austin MC, Fitt GJ, Davis SM, McKay WJ. Reperfusion after thrombolytic therapy in ischemic stroke measured by single-photon emission computed tomography. *Stroke* 1994;25:79–85.
13. Overgaard K, Sperling B, Boysen G, et al. Thrombolytic therapy in acute ischemic stroke. A Danish Pilot Study. *Stroke* 1993;24:1439–1446.
14. Hederschee D, Limburg M, van Royen EA, Hijdra A, Buller HR, Koster PA. Thrombolysis with recombinant tissue plasminogen activator in acute ischemic stroke: evaluation with rCBF-SPECT. *Acta Neurol Scand* 1991;83:317–322.
15. Hanson SK, Grotta JC, Rhoades H, Tran HD, Lamki LM, Barron BJ, Taylor WJ. Value of single-photon emission computed tomography in acute stroke therapeutic trials. *Stroke* 1993;24:1322–1329.
16. Lassen NA. The luxury-perfusion syndrome and its possible relations to acute metabolic acidosis localized within the brain. *Lancet* 1966;ii:1113–1115.
17. Infeld B, Davis SM, Donnan GA, et al. Streptokinase increases luxury perfusion after stroke. *Eur J Neurol* 1995;2(suppl. 2):8–9.
18. Davis SM, Chua MG, Lichtenstein M, Rossiter SC, Binns D, Hopper JL. Cerebral hypoperfusion in stroke prognosis and brain recovery. *Stroke* 1993;24:1691–1696.
19. Infeld B, Davis SM, Lichtenstein M, Mitchell PJ, Hopper JL. Crossed cerebellar diaschisis and brain recovery from stroke. *Stroke* 1995;26:90–95.
20. Giubilei F, Lenzi GL, Di Piero V, et al. Predictive value of brain perfusion single-photon emission computed tomography in acute ischemic stroke. *Stroke* 1990;21:895–900.
21. Brass LM, Walovitch R, Joseph J, et al. The role of single-photon emission computed tomography brain imaging with ^{99m}Tc-bisicate in localization and definition of mechanism of ischemic stroke. *J Cereb Blood Flow Metab* 1994;14:91–98.
22. Alexandrov AV, Ehrlich LE, Black SE, Norris JW. HMPAO-SPECT scanning in acute stroke [Abstract]. *Cerebrovasc Dis* 1995;5:253.

23. Cote R, Battista RN, Wolfson C, Boucher J, Adam J, Hachinski V. The Canadian Neurological Scale: validation and reliability assessment. *Neurology* 1989;39:638–643.
24. Laloux P, Richelle F, Jamart J, de Coster P, Laterre C. Comparative correlations of HMPAO-SPECT indices, neurological score and stroke subtypes with clinical outcome in acute carotid infarcts. *Stroke* 1995;26:816–821.
25. Lisk DR, Grotta JC, Lamki LM, Tran HD, Taylor JW, Molony DA, Barron BJ. Should hypertension be treated after acute stroke? A randomized controlled trial using single-photon emission computed tomography. *Arch Neurol* 1993;50:855–862.
26. Alexandrov AV, Bladin CF, Ehrlich LE, Norris JW. Noninvasive assessment of intracranial perfusion in acute cerebral ischemia. *J Neuroimaging* 1995;5:76–82.
27. Limburg M, van Royen EA, Hijdra A, Verbeeten B Jr. rCBF-SPECT in brain infarction: when does it predict outcome? *J Nucl Med* 1991;32:382–387.
28. Shimosegawa E, Hatazawa J, Inugami A, et al. Cerebral infarction within six hours of onset: prediction of completed infarction with technetium-99m-HMPAO SPECT. *J Nucl Med* 1994;35:1097–1103.
29. Mehler AH. Amino acid metabolism II: metabolism of individual amino acids. In: Devlin TM, ed. *Textbook of biochemistry with clinical correlations*, 3rd ed. New York: Wiley-Liss; 525.
30. Report of the Therapeutics and Technology Assessment Subcommittee of the American Academy of Neurology. Assessment of brain SPECT. *Neurology* 1996;46:278–285.