

A Metabolic Imaging Severity Rating Scale for the Assessment of Cognitive Impairment

ANDREW NEWBERG, M.D.,* ADOLFO COTTER,* MICHELLE UDESHI,* ABASS ALAVI,* AND CHRISTOPHER CLARK†

Purpose: This study was designed to validate a simple scoring system for evaluating fluorodeoxyglucose (FDG) positron emission tomographic (PET) scans that can be used routinely in patients undergoing the clinical assessment of cognitive impairment.

Methods: The FDG-PET scans of 106 patients with cognitive impairment (65 with Alzheimer disease, 16 with frontal lobe dementia, and 25 atypical cases) were acquired using the PENN-PET scanner 40 minutes after the intravenous administration of 8 mCi FDG. Metabolic activity in various anatomic structures of the brain was scored using the following qualitative scale: 4 = normal; 3 = mildly decreased; 2 = moderately decreased; 1 = severely decreased; and 0 = no activity. Regions of interest were also placed over these regions to obtain a quantitative value. Two distinct scores were obtained. Values for visual and sensorimotor cortices, thalami, basal ganglia, and cerebellum comprised score I. Score II consisted of the values for the frontal, temporal, and parietal cortices. The qualitative metabolic imaging severity rating scale (MISRS) was compared with a quantitative MISRS (obtained from the region-of-interest analysis of the same structures). The MISRS was then compared with the results from the Mini-Mental Status Examination (MMSE) and the Dementia Severity Rating Score (DSRS).

Results: In all patients, the qualitative MISRS scores correlated significantly with the quantitative MISRS ($r = 0.73$, $P < 0.0001$). In all patients with cognitive impairment, the qualitative and quantitative MISRS scores correlated significantly with the DSRS and the MMSE ($P < 0.001$). In patients with Alzheimer disease, the qualitative and quantitative MISRS significantly correlated with the DSRS and MMSE.

Conclusion: A simple and practical rating scale can be used to assess the severity of cognitive impairment in patients with different types of dementing illnesses.

Key Words: Cerebral Metabolism, Cognitive Impairment, Positron Emission Tomography.

From the Division of Nuclear Medicine, Department of Radiology, and the Department of Neurology,† Hospital of the University of Pennsylvania, Philadelphia, Pennsylvania*

INVESTIGATORS IN SEVERAL previous positron emission tomography (PET) studies have tried to develop reliable and reproducible methods for evaluating scan findings and correlating these findings with the degree of patient cognitive impairment. Clearly, clinical assessment of patients that includes a neuropsychological evaluation is essential for diagnosing dementia and determining the extent of cognitive dysfunction. More recently, statistical parametric mapping has been used in the analysis of patients with Alzheimer disease (AD) and related disorders (1,2). However, the statistical parametric mapping method has not attained wide application clinically, although it is now used extensively for research purposes. Standardized uptake values of the whole brain and various regions have been only marginally successful in clearly identifying patients with AD (3). Many previous studies have used various combinations of imaging studies, clinical findings, and physiologic measures to determine how to differentiate AD from other types of dementia such as frontal lobe dementia (FD) and how to follow the course of the disease over time (4-7). The ability to differentiate between the different dementing illnesses is pertinent but was not the primary focus of this study.

In this study, a new clinical scoring system for PET scans that can be used by any nuclear medicine practitioner is tested. This Metabolic Imaging Severity Rating Scale (MISRS) is based on the clinical reading of PET scans resulting in a qualitative scoring system that can be used to assess overall cerebral function and ultimately correlate that function to clinical status. Therefore, the MISRS needs to be compared with measures of the level of cognitive dysfunction such as the Mini-Mental State Exam (MMSE) and the Dementia Severity Rating Score (DSRS). The DSRS is a functional measurement incor-

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Correspondence: Andrew B. Newberg, Division of Nuclear Medicine, Hospital of the University of Pennsylvania, 110 Donner Building, 3400 Spruce Street, Philadelphia, Pennsylvania 19104. E-mail: newberg@rad.upenn.edu

porating both cognitive impairment and activities of daily living. By using these measures, we tried to develop a reliable and reproducible method for evaluating patients and diagnosing possible dementia.

The first hypothesis to be tested as part of this study was to demonstrate a strong correlation between the qualitative MISRS and a quantitative MISRS that is based on region-of-interest analysis of the same areas involved in the qualitative MISRS. The ability to confirm the findings of the clinical scores with those derived quantitatively helps to establish this method of evaluating clinical PET scans. The second hypothesis was that the qualitative MISRS would correlate strongly with the degree of cognitive impairment as measured by the MMSE and DSRS. The third hypothesis was that the MISRS would correlate with cognitive impairment (MMSE and DSRS) in each of a variety of dementing illnesses. The fourth hypothesis was that the MISRS would successfully distinguish between different dementing illnesses. By testing each of these hypotheses, we wanted to show that the MISRS is successful in evaluating fluorodeoxyglucose (FDG)-PET brain scans by matching quantitative data, correlating with disease severity, and differentiating diagnoses.

Materials and Methods

Patient Selection

We recruited 106 patients from the Department of Neurology at the University of Pennsylvania who had progressive cognitive decline. All subjects provided informed consent that was approved, along with the protocol, by the University of Pennsylvania Institutional Review Board. A subset of 65 patients were given the diagnosis of probable AD based on the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) Work Group (8) criteria. Another group of 16 patients was thought to have FD based on clinical and neuropsychological criteria. A third group of 25 patients who did not meet the criteria for AD or FD were considered to have atypical dementia. Patients were included in the study if the results of their medical history, physical examination, and laboratory studies were not indicative of any other underlying disease process that could have caused or maintained the dementing illness. Patients were given an MMSE, with possible scores of 0 (severely demented) to 30 (normal), and a DSRS score in which the higher the score, the worse the cognitive impairment. This score has been described previously and is a functional measurement incorporating both cognitive impairment and activities of daily living (9).

Positron Emission Tomographic Imaging

The PET images were acquired according to previously described methods (10). Briefly, intravenous and intra-arterial catheters were inserted with the patient under local anesthesia. The patient's eyes were open, ears were unoccluded, and ambient noise was kept to a minimum during the study. The

patients were then injected with 8 mCi/70 kg FDG. The PET images were acquired 40 minutes after the administration of FDG. Images were obtained using the PENN-PET scanner with a resolution of 5.5 mm in all three planes. The head was fixed in place throughout the study by a head holder, and an investigator or technologist monitored the correct position. When scanning was complete, the images were reconstructed in the transaxial planes using an optimized Hanning filter. Attenuation correction was performed by applying Chang's method (11).

Image Analysis and Calculation of the MISRS

All FDG-PET scans were interpreted by two experienced reviewers blinded to any clinical information. The metabolic activity of each anatomic structure on the PET scan was also given a score: 4 = normal activity; 3 = mildly decreased activity; 2 = moderately decreased, 1 = severely decreased; and 0 = no activity. The MISRS is comprised of two scores based on the areas commonly associated with cognitive impairment, specifically the cortical association areas. The structures used are also observed to be those most affected in dementing illnesses such as AD. Score I was calculated as the sum of the visual cortex, sensorimotor cortex, thalami, cerebellum, and the basal ganglia (these areas are not typically associated with cognitive impairment). Score II was calculated as the sum of the frontal, temporal, and parietal cortices (these are the areas typically associated with cognitive impairment). The MISRS was calculated using the following formula: $200 \times (\text{score I} - \text{score II}) / (\text{score I} + \text{score II})$. The result is the percentage difference between the activity in the areas typically affected in cognitively impaired patients and those not typically affected. A score of 50 is normal (i.e., all brain regions have a score of 4), and the higher the score, the more affected are the frontal, temporal, and parietal cortices (Figs. 1 and 2).

Quantitative MISRS Determination

For comparison, a template was designed with regions of interest that measured the mean number of counts in the regions included in both score I and score II, described above. These quantitatively derived values could then be used to calculate a quantitative MISRS, which could be compared with the MISRS determined by the qualitative scoring system. This allowed for quantitative verification of the qualitative MISRS.

Statistical Analyses

A linear regression model and a Spearman rank correlation were calculated for the MISRS, the MMSE, and the DSRS. Correlations were also determined between the quantitatively derived MISRS and the qualitatively derived MISRS. Furthermore, correlations were determined for the quantitatively derived MISRS, the MMSE, and the DSRS.

Results

In testing the first hypothesis, the quantitative and qualitative MISRS scores were compared (Fig. 3). The qualitative and quantitative MISRS scores correlated with each other significantly ($r = 0.73$; $P < 0.0001$), thus validating this subjective semiquantitative scoring method.

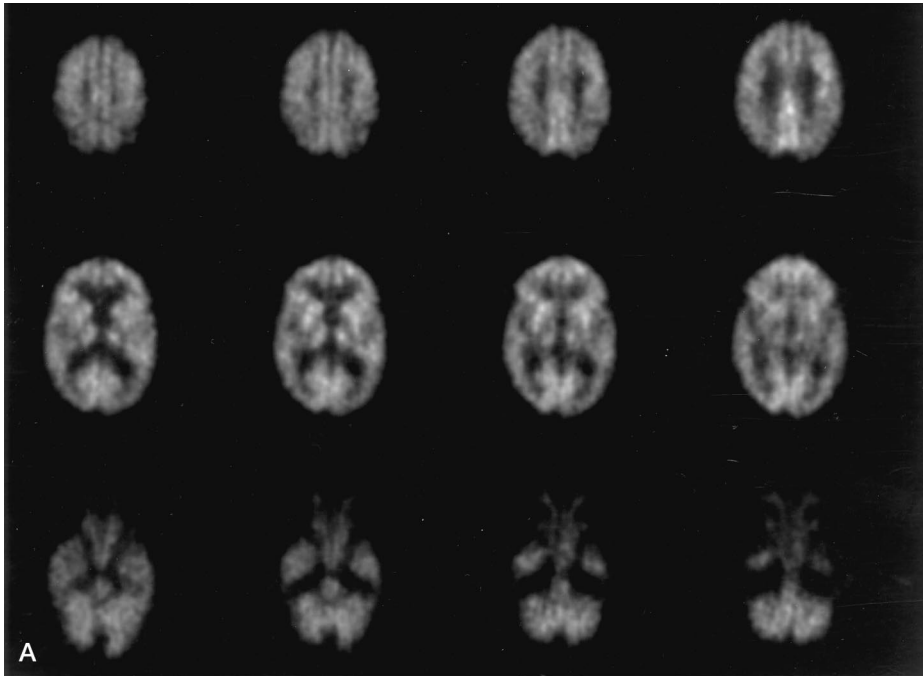


Fig. 1. (a) An FDG-PET scan from a patient with mild AD shows mildly decreased activity in both temporoparietal regions. (b) The corresponding MISRS scoring sheet is included for this patient.

Score I		
Right Basal Ganglia		<u>4</u>
Left Basal Ganglia		<u>4</u>
Right Cerebellum		<u>4</u>
Left Cerebellum		<u>4</u>
Right Thalamus		<u>4</u>
Left Thalamus		<u>4</u>
Right Visual Area		<u>4</u>
Left Visual Area		<u>4</u>
Right Sensorimotor		<u>4</u>
Left Sensorimotor		<u>4</u>
Total Score I		<u>40</u>
Score II		
Right Frontal		<u>4</u>
Left Frontal		<u>4</u>
Right Temporal		<u>3</u>
Left Temporal		<u>3</u>
Right Parietal		<u>3</u>
Left Parietal		<u>3</u>
Total Score II		<u>20</u>
MISRS		
Score I - Score II	* 200	<u>67</u>
Score I + Score II		

B

Evaluation of our second hypothesis revealed that in all patients, both the qualitative and quantitative MISRS correlated significantly with the MMSE and the DSRS, although the quantitative MISRS had slightly better cor-

relations (Table 1). More specifically, in the AD subgroup of patients, the qualitative MISRS correlated significantly with the MMSE ($r = 0.47, P < 0.01$) and the DSRS ($r = -0.27, P < 0.05$). Similar, but slightly stronger

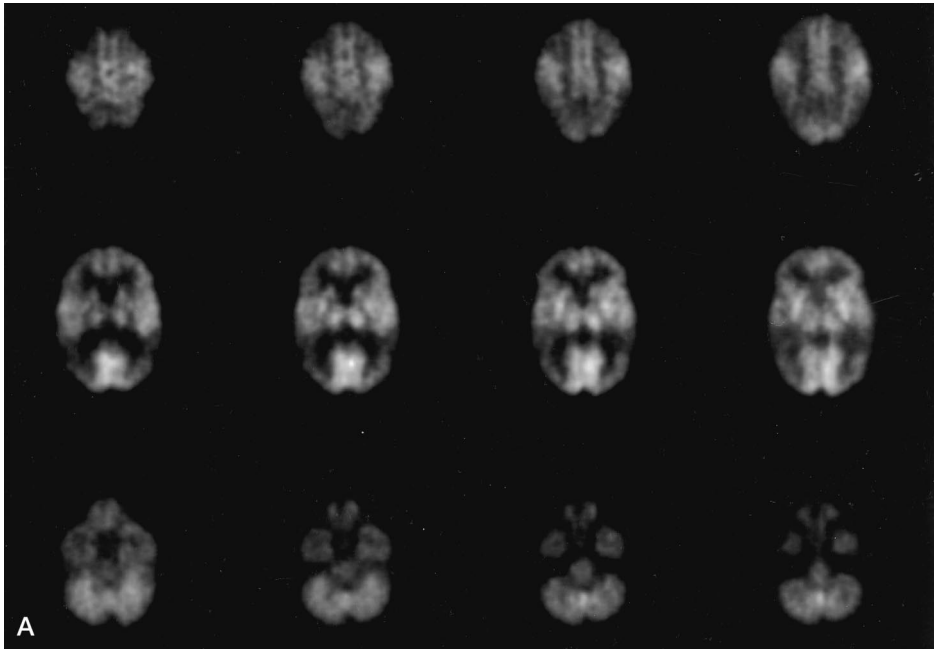


Fig. 2. (a) An FDG-PET scan from a patient with severe AD shows severely decreased activity in both temporoparietal regions and both frontal lobes, with relative preservation of the sensorimotor area, visual cortex, subcortical structures, and cerebellum. (b) The corresponding MISRS scoring sheets is included for this patient.

Score I		
Right Basal Ganglia		<u>4</u>
Left Basal Ganglia		<u>4</u>
Right Cerebellum		<u>4</u>
Left Cerebellum		<u>4</u>
Right Thalamus		<u>4</u>
Left Thalamus		<u>4</u>
Right Visual Area		<u>4</u>
Left Visual Area		<u>4</u>
Right Sensorimotor		<u>4</u>
Left Sensorimotor		<u>4</u>
Total Score I		<u>40</u>
Score II		
Right Frontal		<u>1</u>
Left Frontal		<u>1</u>
Right Temporal		<u>2</u>
Left Temporal		<u>2</u>
Right Parietal		<u>1</u>
Left Parietal		<u>1</u>
Total Score II		<u>8</u>
MISRS		
Score I-Score II	* 200	<u>133</u>
B Score I + Score II		

correlations were observed between the quantitative MISRS and the clinical scores. In patients with FD, the qualitative MISRS was not as successful, with marginally significant correlations with the MMSE ($r = 0.5, P = 0.04$) and no significant relation with the DSRS. In pa-

tients with atypical dementia, the quantitative MISRS was significantly correlated with the MMSE ($r = 0.52, P < 0.01$) and DSRS ($r = -0.55, P < 0.01$), although the qualitative MISRS did not correlate significantly with either of the test results.

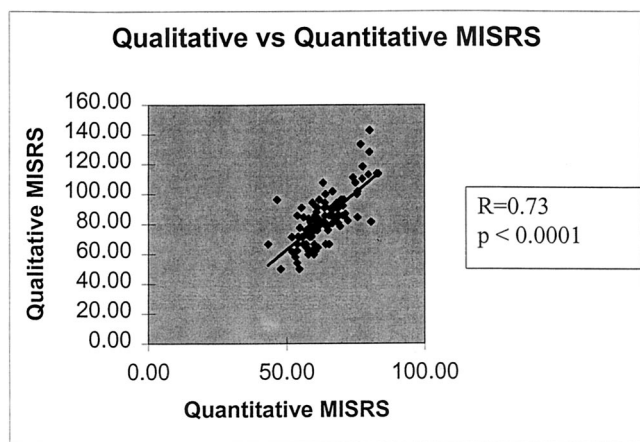


Fig. 3. A plot compares quantitative and qualitative MISRS scores for all patients with cognitive impairment.

These findings indicate that patients who function poorly as determined by the DSRs or MMSE tend to have greater metabolic deficits in the frontal, temporal, and parietal cortices and that this is particularly true in patients with AD compared with those with FD or other dementing illnesses. With regard to the third hypothesis, the results of this study show that the qualitative MISRS correlated with the degree of cognitive impairment in patients with AD and FD but did not do as well in the atypical population. This suggests that the qualitative MISRS is better for evaluating patients with AD and FD.

The MISRS did not adequately distinguish the clinical diagnosis of AD from FD or from the atypical demen-

tias. However, histopathologic diagnoses were not obtained, so we could not determine whether the PET findings or the clinical findings represent the most accurate diagnosis.

Discussion

In this study, a new metabolic scoring system of PET scans, the Metabolic Imaging Severity Rating Scale, was tested. The reason for calculating this scale in the manner described here was based on the association areas typically affected in patients with cognitive impairment, particularly AD. Because AD typically involves the temporal and parietal areas (12–15), with the frontal lobes involved in more severe cases, and because these regions are also involved in higher cognitive processes, these regions might be combined (score II) to measure the metabolic dysfunction in such patients. By comparing score II with those areas not typically associated with cognitive impairment (score I), we hoped the MISRS would provide a method for evaluating patients with different dementing illnesses in the clinical setting.

In addition, this type of rating scale would be a useful clinical tool for assessing and following patients with dementing illnesses. Therefore, to ensure that the qualitative MISRS would be a reliable measure of metabolic dysfunction, we compared it with a quantitative MISRS. The results of this study indicate that the qualitative MISRS matches quantitative data, thus supporting the first hypothesis for this study. This suggests that the qualitative MISRS would be an accurate clinical scoring system that could potentially be reported to referring physicians to help in their assessment of patients with cognitive impairment.

Studies correlating cerebral glucose metabolism to MMSE scores and other neuropsychological testing have more consistently shown a relation between these measures in patients with AD. This is particularly true when parietal and temporal lobe metabolic rates (involved in AD) have been compared with neuropsychological deficits. In patients with AD of varying severity, the magnitude and extent of hypometabolism on functional neuroimaging has been shown to correlate with the severity of the dementia symptoms (16). These studies indicated that in patients with early AD, there are no significant metabolic changes or only minor decreases in the parietal lobes. Moderately affected patients show significantly decreased metabolism in the bilateral parietal lobes and the superior temporal regions. In patients with severe AD, the same regions are affected, but the hypometabolism is much more pronounced. Longitudinal studies have shown that cerebral glucose metabolism decreases more rapidly over time in patients with AD than in age-matched controls (17). There is also a more

TABLE 1. Comparison Between the Qualitative and Quantitative MISRS to MMSE and DSRs

	MMSE		DSRS	
	R	P	R	P
All Cases (n = 106)				
Qualitative MISRS	0.46	<0.001	-0.26	<0.001
Quantitative MISRS	0.56	<0.001	-0.37	<0.001
AD Cases (n = 65)				
Qualitative MISRS	0.47	<0.01	-0.27	<0.05
Quantitative MISRS	0.59	<0.01	-0.37	<0.01
FD Cases (n = 16)				
Qualitative MISRS	0.50	0.04	-0.10	N.S.
Quantitative MISRS	0.46	0.062	-0.04	N.S.
Atypical Cases (n = 25)				
Qualitative MISRS	0.28	N.S.	-0.28	N.S.
Quantitative MISRS	0.52	<0.01	-0.55	<0.01

MISRS, metabolic imaging severity rating scale; MMSE, Mini-Mental Status Exam; DSRs, Dementia Severity Rating Score.

severe decrement in parietal lobe metabolism compared with frontal lobe metabolism over time.

Because studies have shown a correlation between the extent of hypometabolism and the severity of cognitive dysfunction, we expected the MISRS to correlate well with cognitive scores such as the DSRS and MMSE. In this study, the MISRS correlated with measures of cognitive impairment in all patients, thus validating our second hypothesis. However, this correlation was strongest for patients with AD and weakest for atypical cases. Therefore, the results of this study indicate that, regarding the third hypothesis, the MISRS does correlate with cognitive deficits in each type of dementia, but to varying degrees. Accordingly, this scale can provide important management information in patients with AD and, to a lesser extent, in patients with other dementias.

With the development of new pharmacologic methods for the treatment of AD versus other types of dementing illnesses, it is important to differentiate between them. It has not been possible to distinguish AD patients from those with non-Alzheimer's dementia based on quantitative measurement of absolute whole-brain metabolism (18). In the current study, testing of the fourth hypothesis revealed that the MISRS did not adequately distinguish the clinical diagnosis of AD from other types of dementing illnesses. However, without a histopathologic diagnosis, we do not know whether the PET findings or the clinical findings represent the most accurate diagnosis. In addition, the MISRS may have diminished success in evaluating patients with cognitive impairment because areas such as the sensorimotor and visual cortices, subcortical nuclei, brain stem, and cerebellum may be abnormal when there is a specific neuropsychological deficit (19–21).

In conclusion, the MISRS may provide a useful clinical tool, especially for referring physicians who may benefit from having more specific semiquantitative information regarding their patients with cognitive impairment. Expansion of the use of this clinical tool may include use in other dementia-related disorders and possibly in the evaluation of SPECT studies. Furthermore, the MISRS may help clinicians follow their patients over time to determine which patients have the most severe metabolic deficits and which patients may respond to therapeutic interventions aimed at attenuating the effects of dementing illnesses.

References

1. Johannsen P, Jakobsen J, Gjedde A: Statistical maps of cerebral blood flow deficits in Alzheimer's disease. *Eur J Neurol* 7:385, 2000.

2. Ishii K, Sasaki M, Matsui M, et al: A diagnostic method for suspected Alzheimer's disease using H(2)15O positron emission tomography perfusion Z score. *Neuroradiology* 42:787, 2000.
3. Yamaji S, Ishii K, Sasaki M, et al: Evaluation of standardized uptake value to assess cerebral glucose metabolism. *Clin Nucl Med* 25:11, 2000.
4. Jelic V, Nordberg A: Early diagnosis of Alzheimer disease with positron emission tomography. *Alzheimer Dis Assoc Disord* 14(Suppl 1):S109, 2000.
5. Pietrini P, Alexander GE, Furey ML, et al: The neurometabolic landscape of cognitive decline: in vivo studies with positron emission tomography in Alzheimer's disease. *Int J Psychophysiol* 37:87, 2000.
6. Small GW, Ercoli LM, Silverman DH, et al: Cerebral metabolic and cognitive decline in persons at genetic risk for Alzheimer's disease. *Proc Natl Acad Sci U S A* 97:6037, 2000.
7. Berent S, Giordani B, Foster N, et al: Neuropsychological function and cerebral glucose utilization in isolated memory impairment and Alzheimer's disease. *J Psychiatr Res* 33:7, 1999.
8. McKhann G, Drachman D, Folstein M, et al: Clinical diagnosis of Alzheimer's disease: report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. *Neurology* 34:939, 1984.
9. Clark CM, Ewbank DC: Performance of the dementia severity rating scale: a caregiver questionnaire for rating severity in Alzheimer disease. *Alzheimer Dis Assoc Disord* 10:31, 1996.
10. Karp JS, Muehllehner G, Mankoff DA, et al: Continuous-slice PENN-PET: a positron tomograph with volume imaging capability. *J Nucl Med* 31:617, 1990.
11. Chang LT: A method for attenuation correction in radionuclide computed tomography. *IEEE Trans Nucl Sci* 25:638, 1978.
12. Kumar A, Newberg AB, Alavi A, et al: MRI volumetric measures in Alzheimer's disease: relationship to clinical and neuropsychological variables. *Am J Geriatr Psychiatr* 2:21, 1994.
13. Dickerson BC, Goncharova I, Sullivan MP, et al: MRI-derived entorhinal and hippocampal atrophy in incipient and very mild Alzheimer's disease. *Neurobiol Aging* 22:747, 2001.
14. Sencakova D, Graff-Radford NR, Willis FB, et al: Hippocampal atrophy correlates with clinical features of Alzheimer disease in African Americans. *Arch Neurol* 58:1593, 2001.
15. De Santi S, de Leon MJ, Rusinek H, et al: Hippocampal formation glucose metabolism and volume losses in MCI and AD. *Neurobiol Aging* 22:529, 2001.
16. Foster NL, Chase TN, Mansi L, et al: Cortical abnormalities in Alzheimer's disease. *Ann Neurol* 16:649, 1984.
17. Jagust WJ, Friedland RP, Budinger TF, et al: Longitudinal studies of regional cerebral metabolism in Alzheimer's disease. *Neurology* 38:909, 1988.
18. Newberg A, Alavi A, Souder E, et al: A comparison of FDG-PET and MRI data from patients with atypical dementias and Alzheimer's disease (AD) [Abstract]. *J Nucl Med* 33:965, 1992.
19. Hirono N, Mori E, Ishii K, et al: Regional hypometabolism related to language disturbance in Alzheimer's disease. *Dement Geriatr Cogn Disord* 9:68, 1998.
20. Cummings JL: Cognitive and behavioral heterogeneity in Alzheimer's disease: seeking the neurobiological basis. *Neurobiol Aging* 21:845, 2000.
21. Shinosaki K, Nishikawa T, Takeda M: Neurobiological basis of behavioral and psychological symptoms in dementia of the Alzheimer type. *Psychiatr Clin Neurosci* 54:611, 2000.