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Seminars in
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MEDICINE

2-Deoxy-Fluorglucose–Positron Emission Tomography Imaging of the Brain: Current Clinical Applications with Emphasis on the Dementias

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A number of very significant advances in the field of positron emission tomography (PET) imaging are now beginning to have an impact on clinical PET brain imaging. Among the most significant advances are further improvements in PET scanner detectors and computers. Increasingly, more sophisticated methods of image analysis and quantitation are also beginning to emerge. In addition, there has been a very rapid introduction of newer PET radiotracers that will ultimately work their way into the clinical environment. Finally, there is an expanding interest in the potential of PET brain imaging in the evaluation of a wide variety of clinical neuropsychiatric conditions.
Semin Nucl Med 34:300-312

Positron emission tomography (PET) brain imaging is beginning to experience significant growth in the number of procedures being performed. This is because of the greater availability of imaging facilities, commercial radiopharmacies, and the increasing use of combined PET-MR fusion studies. There is also a growing recognition that PET imaging provides unique pathophysiologic information for a number of neurologic and psychiatric disorders.

PET: Radiotracers and Instrumentation

PET imaging with 2-deoxy-fluorglucose (FDG-PET) is very useful in the evaluation of regional glucose metabolism in a variety of neurological disorders.[1] The availability of FDG has been enhanced by the introduction of commercial PET. Radiopharmacies using automated production methods are now capable of distributing FDG throughout the United States. In general, FDG follows the glycolytic pathway to the level of phosphorylation, where it remains trapped for an extended period of time.[2] The distribution of FDG is thus an accurate measure of regional brain glucose metabolic activity. Other PET radiotracers, such as $[^{15}O]H_2O$ and $[^{15}O]O_2$, have been used to assess regional cerebral blood flow, oxygen consumption, and oxygen extraction fraction.[3,4] In addition, ^{11}C and ^{18}F radiotracers also have been used to evaluate neuroreceptor function and physiology.[5,6]

PET instrumentation developments have also been very exciting. At present, high-resolution PET scanners using bismuth gadolinium oxylate crystal detector technology with spatial resolution in the range of 4-mm (FWHM) represent "state-of-the-art" capability. The rapid growth in PET instrumentation availability is related in part to lower cost imaging devices coupled with new image reconstruction algorithms and improved performance computer technology. Newer PET scanners incorporating alternative detector crystal technology, such as leutium orthodoxy silicate and gadolinium oxyorthosilicate detectors, have recently become more widely available.[7] PET is increasingly being combined with three-dimensional acquisition modes that result in faster patient throughput and/or reduced patient dose. Other technological advances have included the development of combined PET-CT scanners, which allow for concurrent PET and CT scans to be performed.[8] In the future, it is likely that other hybrid scanner technologies such as combined PET-MR will emerge.

PET: Technique

It is helpful to start an intravenous line approximately 10 min before the administration of the radiotracer. This approach helps to minimize patient anxiety regarding the procedure and, in particular, anticipation of the radiopharmaceutical injection. At the time of radiotracer administration, the patient should be in a quiet area, with ambient temperature and light. A standard injection protocol should routinely be used. At our institution, patients are injected with their eyes open, staring at crossed lines and with unplugged ears.

FDG-PET doses should typically be in the range of 5 to 10 mCi (170-370 MBq). In the case of agitated or uncooperative patients, sedation after injection of the radiotracer is preferred over the use of constraining devices. When positioning the patient on the imaging couch, patient comfort is paramount to achieve a successful study.

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 0001-2998/04/$-see frontmatter
doi:10.1053/j.semnuclmed.2004.03.003

Table 1 Positron Emission Tomography Scan Time After Injection

Epilepsy and stroke: 30 min
Dementia: 45 min
Brain tumor: 60 min

The actual imaging time post radiotracer administration will vary according to the patient's age, disease state, clinical indication and stability, (Table 1). PET imaging should, in general, begin 30 to 60 min after the FDG injection.

Brain PET study acquisition will vary with the equipment used and the stability of the patient. Studies should be performed with attenuation correction. Imaging time will vary with the instrumentation and acquisition mode employed. The total imaging time will be in the range of 10 to 20 and 20 to 40 min for three-dimensional (3-D) and two-dimensional (2-D) systems, respectively. In the case of 3-D acquisitions, it is essential that an appropriate head-shielding device be in place to reduce the amount of extra brain scatter radiation that would otherwise degrade the brain images.

The studies should be reviewed before the patient leaves the department. Particular attention should be given to determine if the patient's head is included on all of the images; whether significant patient motion is present, and to ascertain if any of the image data has been lost. If any of these factors has occurred, the study should, whenever possible, be redone before the patient leaves the department. The resultant images should be reconstructed using a filtered back-projection or preferably an iterative reconstruction algorithm.

Normal Brain PET Study

The normal metabolic FDG-PET brain scan differs in subtle but very significant ways from the normal perfusion single-photon emission computed tomography (SPECT) brain scan. A number of technical differences exist between SPECT and PET; the most profound of which relates to differences in spatial and contrast resolution. Typically, the spatial resolution of a high resolution PET scan is in the range of 4 mm (FWHM), whereas a "state-of-the-art" SPECT scanner ranges from 6 to 7 mm (FWHM). This difference translates into an improvement in the ability to distinguish anatomic structures such as the nuclei of the basal ganglia and individual cortical gyri with PET as compared with SPECT. In addition, the degree of radiotracer uptake in the cerebellar gray matter is significantly less on the PET study as compared with a SPECT examination (Fig. 1).

Clinical Indications

The indications for PET brain imaging continue to emerge. The remainder of this review addresses current and future indications in brain tumors, cerebrovascular disease, dementia, head trauma, and epilepsy.

Brain Tumors

Functional brain imaging using nuclear medicine procedures for the evaluation of patients with brain tumors has a long history.[9,10] The initial work using ^{99m}Tc pertechnetate for this purpose was supplanted by SPECT and PET. However, computed tomography (CT) and magnetic resonance imaging (MRI), when introduced, became the procedures of choice. Nevertheless, SPECT and PET continued to play an important clinical role in the diagnosis and management of brain tumors. SPECT studies use the tracers Tl-201, Tc-99m hexamethylpropyleneamine-oxime (HMPAO), and ^{99m}Tc-ethylcystinate dimmer (ECD). Findings based on this technique continue to aid in the diagnosis, prognosis, and management of patients with brain tumor.[11-13] An excellent overview of the application of brain SPECT studies can be found in a review by Mountz and coworkers.[14] At present, SPECT remains a viable tool in tumor evaluation using currently available tracers.

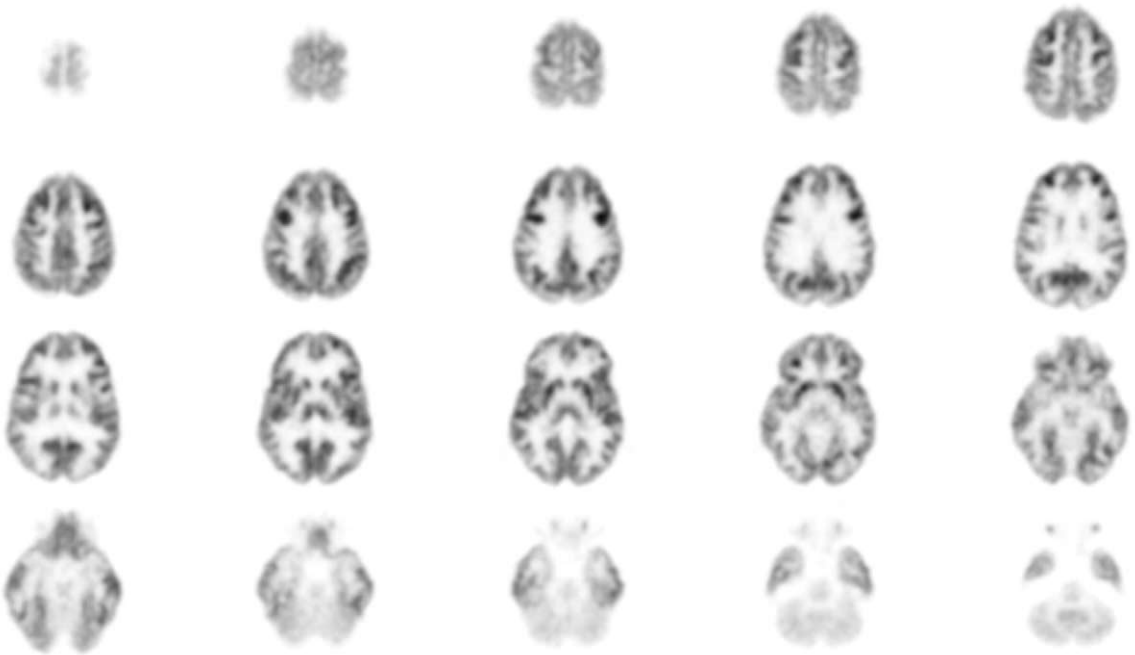


Figure 1 Normal positron emission tomography with 2-deoxy-fluorglucose brain study: Contiguous transverse plane slices, from the vertex of the brain to the cerebellum, demonstrate physiologic regional glucose metabolism in the brain.

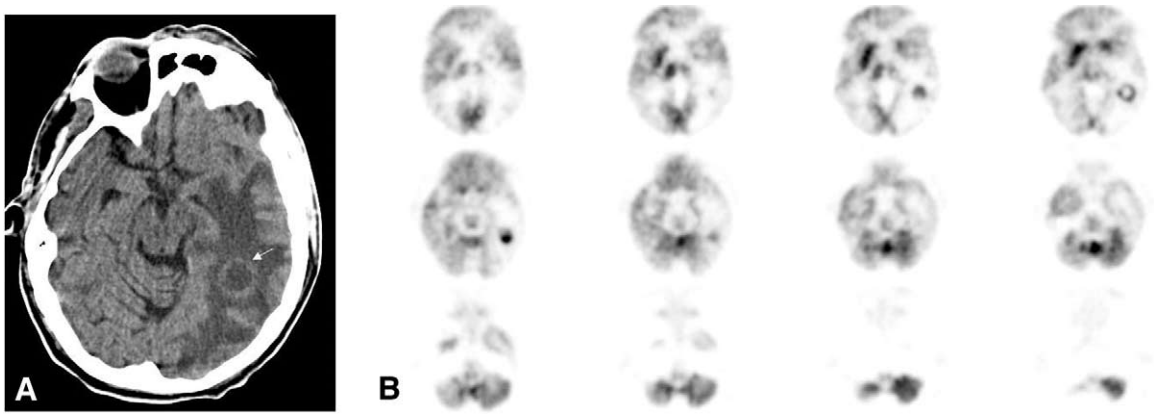


Figure 2 Status after left frontal lobe resection: A 69-year-old man with known metastatic lung cancer with a history of left frontal lobe resection and brain radiation for previous metastatic lesions, now presents with recent onset of seizures. (A) A follow-up head computed tomography scan revealed a left parietal mass lesion (arrow). (B) The subsequent positron emission tomography with 2-deoxy-fluorglucose study demonstrated focal increased peripheral glucose metabolism with central photopenia (arrow) compatible with high-grade malignancy with central necrosis. The diffuse decreased surrounding metabolism is compatible with previous radiation therapy.

SPECT brain imaging was found to helpful in resolving questions of tumor recurrence, viability, the impact of radiation therapy.[15-17] Among the findings reported in the SPECT literature on brain tumors were those attempting to demonstrate the role of dual isotope imaging to help differentiate active from nonactive brain tumors. One study by Schwartz and coworkers[18] found, for example, that this technique might be helpful in separating sites of potential new tumor development from radiation changes in patients under treatment for malignant gliomas. Agents other than Tl-201 and HMPAO have been used for evaluating brain tumors with SPECT. Papazyan and coworkers[19] reported significant differences between SPECT tracers when imaging brain tumors. They report that HMPAO shows greater tracer accumulation than does ECD. A newer agent, ^{99m}Tc tetrofosmin, is reported by Soricelli and coworkers[20] to yield better tumor margin definition and contrast between neoplastic and normal tissue than Tl-201. Although not in wide use, this agent holds promise for providing valuable information on tumor status if SPECT is the only viable functional brain imaging option available.

PET brain tumor imaging did not gain wide acceptance over the past decades because there were few centers that had the necessary imaging capabilities. This situation has undergone significant change. There are increasing numbers of hospital- and nonhospital-based facilities offering PET as an imaging service. The most widely used PET agent, FDG, now is commercially available and delivery of the tracer for routine clinical use is

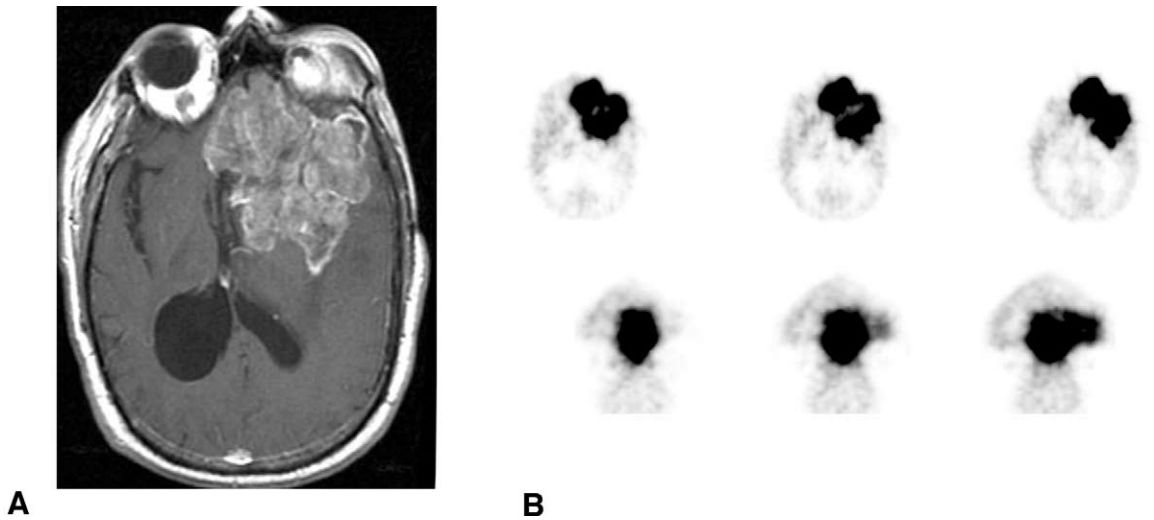


Figure 3 Left frontal lobe oligodendroglioma recurrence: A 56-year-old man with a history of a low-grade left frontal oligodendroglioma is shown. The tumor had been surgically removed and subsequently treated with chemotherapy and radiation. The patient now presents with a recurrent mass lesion at the surgical site. (A) Magnetic resonance imaging (MRI) study revealed the mass lesion in the surgical bed. (B) A follow-up positron emission tomography with 2-deoxy-fluorglucose (axial and coronal plane) scan showed markedly increased radiotracer accumulation in the mass lesion, seen on MRI, compatible with a high-grade malignancy. Pathology showed this to be an anaplastic oligodendroglioma.

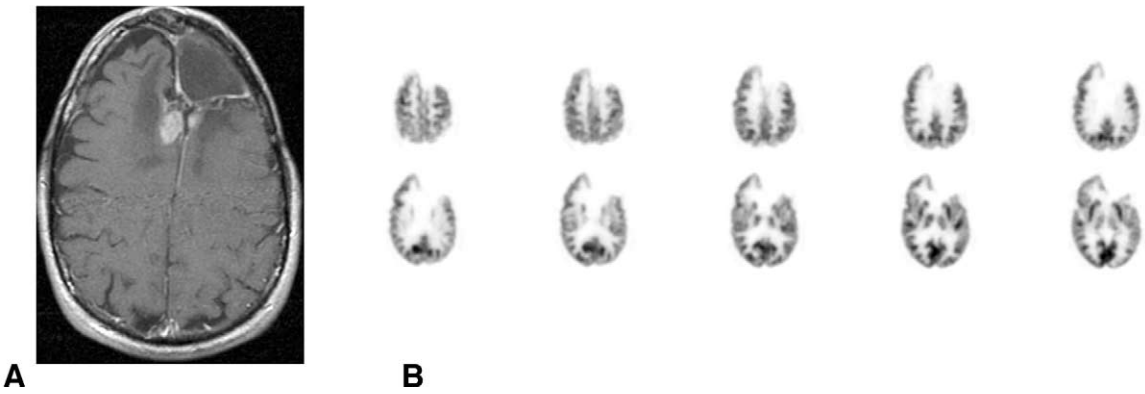


Figure 4 Left frontotemporal oligodendroglioma post treatment: A 52-year-old man with a history of a surgical resection of a left frontotemporal oligodendroglioma followed by chemotherapy and radiation therapy 1 year previously is shown. (A) A follow-up magnetic resonance imaging (MRI) study revealed a mass (arrow) at the site of prior surgery. Differentiation between recurrent tumor and radiation necrosis could not be determined on the MRI examination. (B) A follow-up positron emission tomography with 2-deoxy-fluorglucose scan demonstrated absence of radiotracer uptake compatible with radiation necrosis.

feasible. There has been a growing body of basic and clinical research making a strong case for the use of PET as a technique to evaluate brain tumor patients.[21-25] Results reported in these and other studies demonstrate the role FDG-PET can play in detecting primary brain tumors as well as brain metastases secondary to distant primary tumor sites (Fig. 2). In addition, clinical research also demonstrates the increasing value of FDG-PET in grading tumors, distinguishing new tumor growth from necrosis, or other postradiation effects (Figs. 3 and 4).

There have been some PET studies that have focused on children. Connolly and coworkers[26] note that there has not been as much experience using FDG-PET in children. However, they suggest that now that PET has become more widely available there will be an increase in the application of this technology for studying neuroblastomas and brain tumors in the pediatric population. A recent study[27] compared 18F-fluorodeoxyglucose and relatively new PET tracer 11C-methionine (MET) for characterizing the metabolic activity of brain tumors in children. They

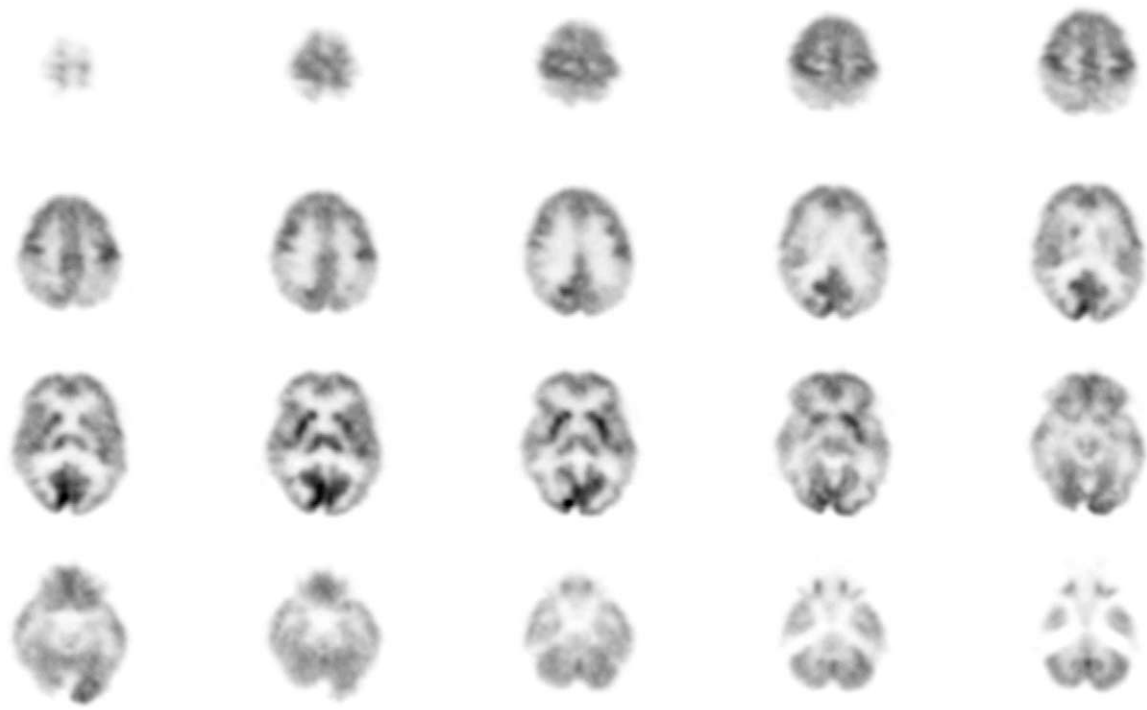


Figure 5 Early dementia: A 64-year-old male presenting with mild memory impairment. A positron emission tomography with 2-deoxy-fluorglucose (A, axial; B, coronal; C, sagittal plane) study demonstrates decreased glucose metabolism in the biparietal and bitemporal lobes with sparing of the primary sensory-motor cortex and visual cortex. The findings are compatible with early Alzheimer's disease.

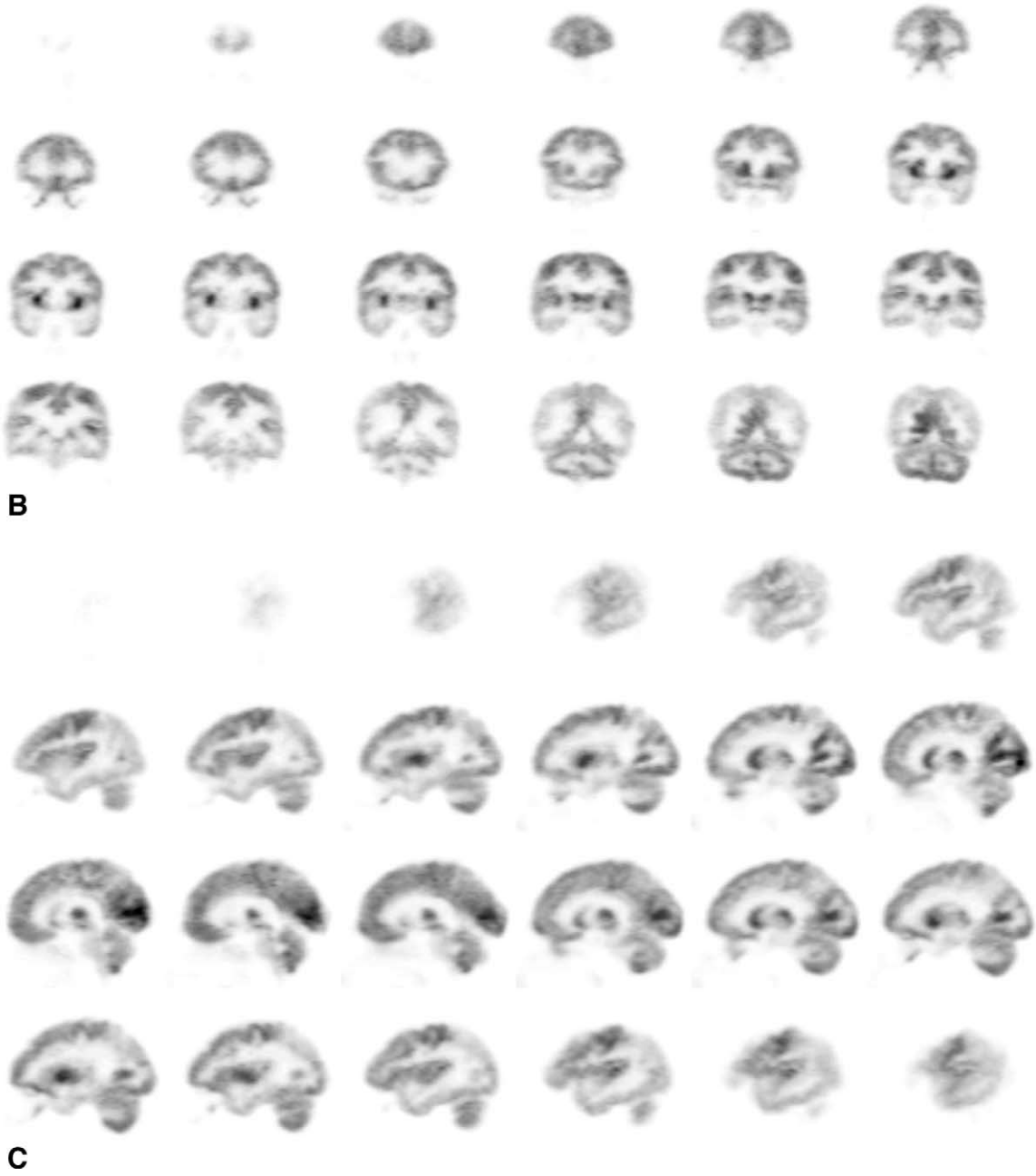


Figure 5 (continued).

found that both tracers are positively correlated with tumor malignancy grade. These authors suggest that there are differences in the information obtained with the two tracers. FDG-PET may be useful in establishing malignancy grade if a histological sample would be difficult to obtain. However, MET-PET delineation of tumor extent may provide additional information that may be helpful in the management of pediatric brain tumors, whether by radiotherapy or surgery. Thus, although Utrianinen and coworkers[27] studied a small sample of patients (n = 27), their conclusions indicate the increasing value of PET for imaging a wide range of patients. Pirotte and coworkers[28] used a combination of MR and PET with FDG or MET for the planning of stereotactic brain biopsies in a small group of children. They report their approach improved the diagnostic yield of stereotactic brain biopsies in infiltrative, ill-defined brain lesions, and reduced the need to take samples from "high-risk" functional brain areas, and that this ultimately "improves the quality of therapeutic management of pediatric brain tumors." As PET technology improves and becomes even more widely available it can be expected that there will be an even greater number of studies to assess the value of this technique in pediatric neurooncology.

In addition to using FDG, an increasing number of studies are being reported where PET is used in combination with MET. In some instances both agents are used because they yield somewhat-different results. Ribom and coworkers[29] report that MET has potential value as a prognostic indicator in patients with low-grade gliomas. Their results show PET can be a "valuable tool in the clinical management of these patients and may assist in the selection of patients for therapy." De Witte and coworkers[30] found that MET uptake was present in 98% of the gliomas they studied. High uptake

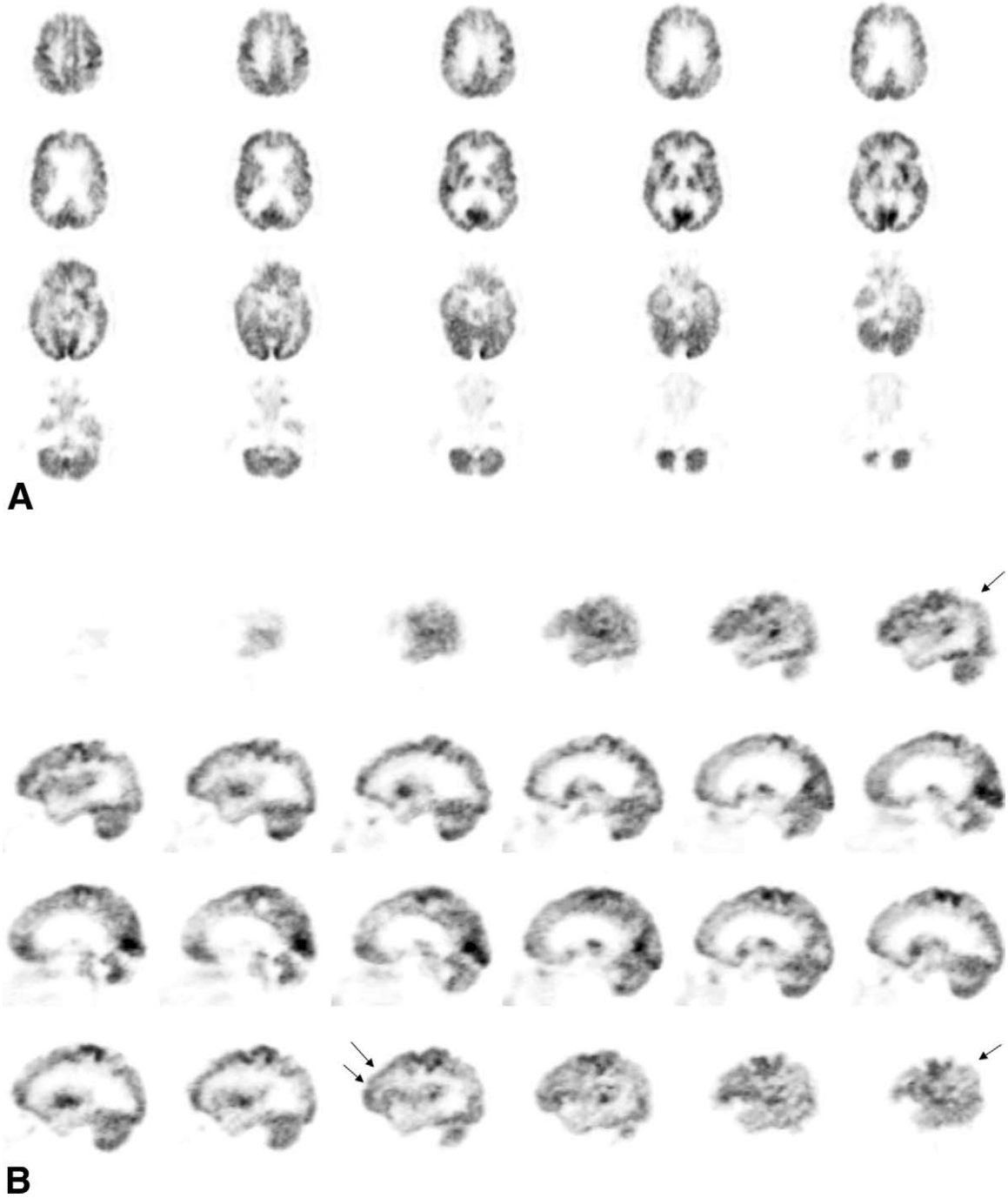


Figure 6 Advanced Alzheimer's disease: A 73-year-old man presenting with a history of progressive cognitive decline over several years. Positron emission tomography with 2-deoxy-fluorglucose (A, axial; B, coronal plane) images show bilaterally decreased glucose metabolism involving the temporal and parietal regions (arrows) with preservation of the sensory-motor cortices and the visual cortex. The frontal lobes (double arrows) also show decreased FDG uptake and the cerebellar glucose metabolism is augmented consistent with advanced Alzheimer's disease.

is correlated with shortened survival time. According to the authors, "the intensity of MET uptake represents a prognostic factor for WHO Grade II and III tumors considered separately." Similar results also were reported by Sorenson and coworkers[31] in a study involving a small group of children. Unfortunately, the use of MET also has some limitation. In particular, the half-life of ^{11}C is very short, making it difficult or even impossible to use this agent in many institutions at the present. However, other agents are being studied that may ultimately overcome this problem.

The coming years will see an increasing number of PET studies using a wider array of imaging agents that have applications to the study of brain tumors. These studies will ultimately determine the role that PET will play in the diagnosis, prognosis, and treatment of patients with brain tumors.

Table 2 Positron Emission Tomography Imaging in Dementia: Clinical Indications

1. Detection
2. Early (preclinical) diagnosis
3. Differential diagnosis
   - Diffuse Lewy body disease
   - Ischemic vascular disease
   - Frontotemporal dementia
   - Huntington's disease
   - Parkinson's disease
   - Creuzfeldt–Jakob disease
   - Pseudodementia of depression
4. Monitor treatment response
5. Follow-up

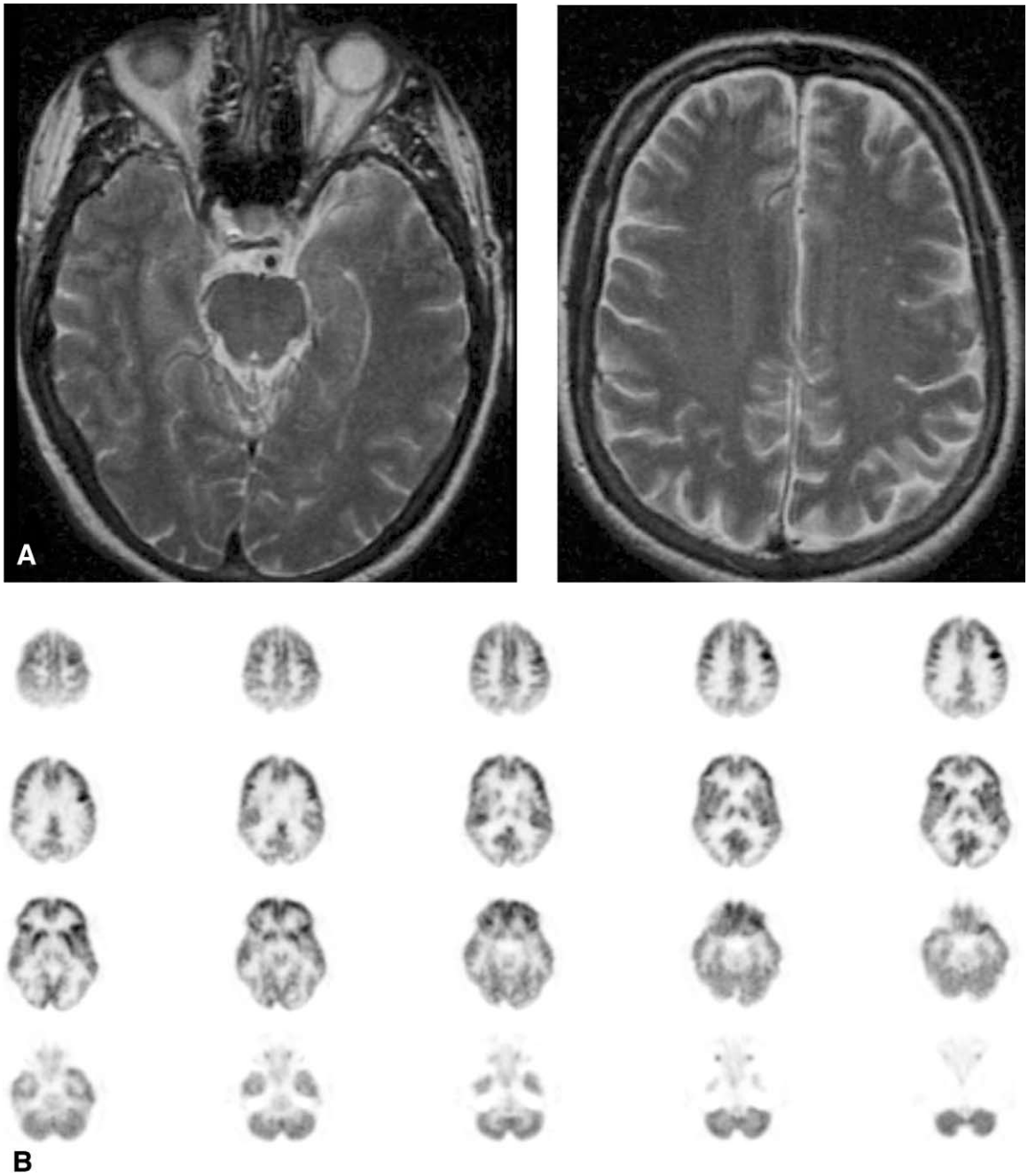
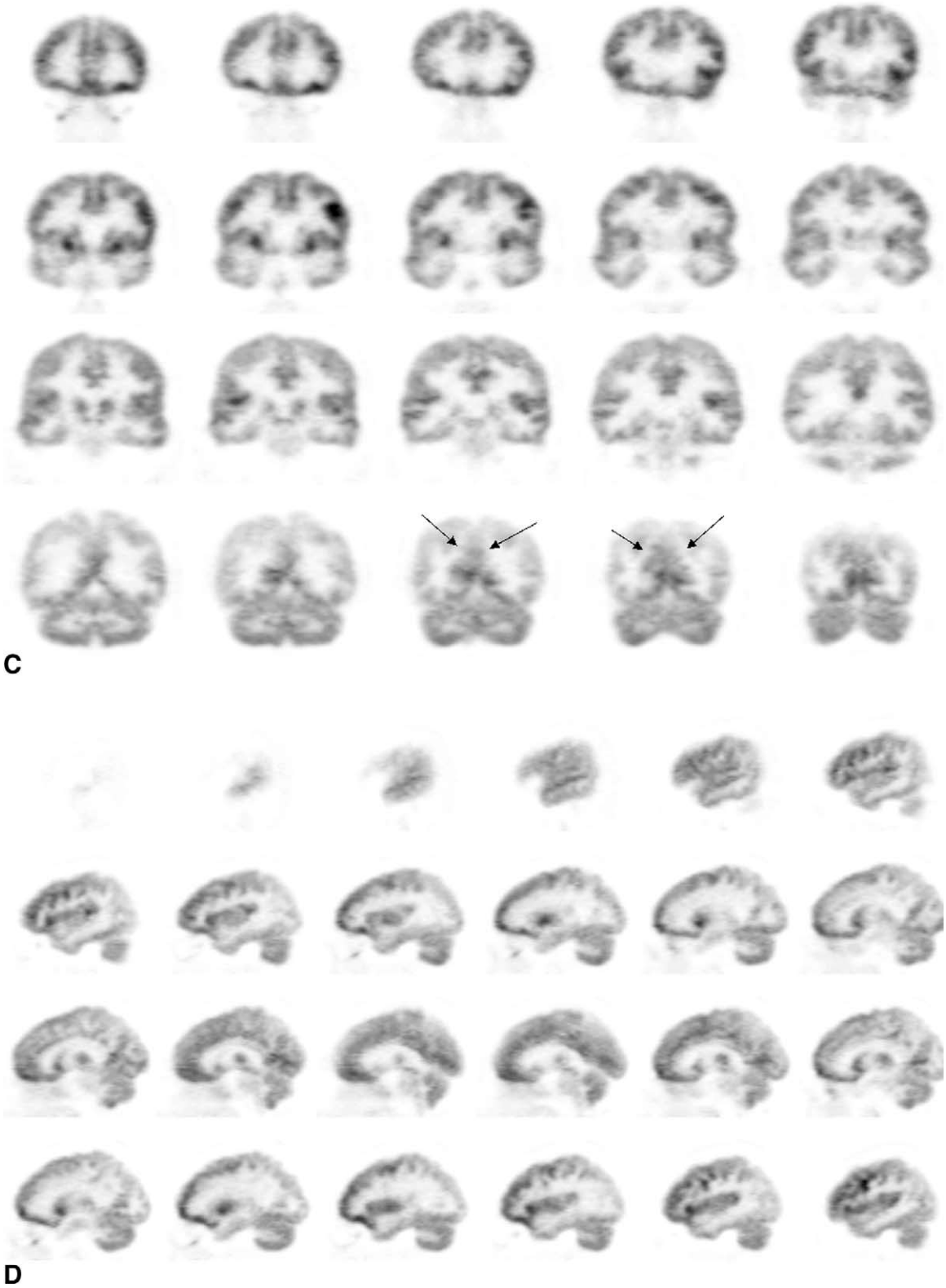


Figure 7 Diffuse Lewy body disease: A 65-year-old man presenting with a history of new-onset visual hallucinations, depression, mild gait disturbance, and progressive cognitive impairment. (A) Magnetic resonance imaging taken 1 week before the positron emission tomography study was unremarkable. (B-D) The positron emission tomography with 2-deoxy-fluorglucose (axial, coronal, sagittal planes) study demonstrates significant bilateral hypometabolism in the temporal and posterior parietal lobes as well as the occipital cortex (arrows).



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Cerebrovascular Disease

The role of PET brain imaging has changed in the past several years. This evolution results from the rapid advances in functional magnetic resonance. In addition, the implementation of more aggressive treatment strategies for the management of acute stroke is impacting the utilization of brain SPECT. Cerebrovascular disease represents a spectrum of disease entities that range from transient ischemia to progressive stroke. Approximately, 400,000 patients sustain acute strokes each year. More than 75% of these are initial strokes and two-thirds are

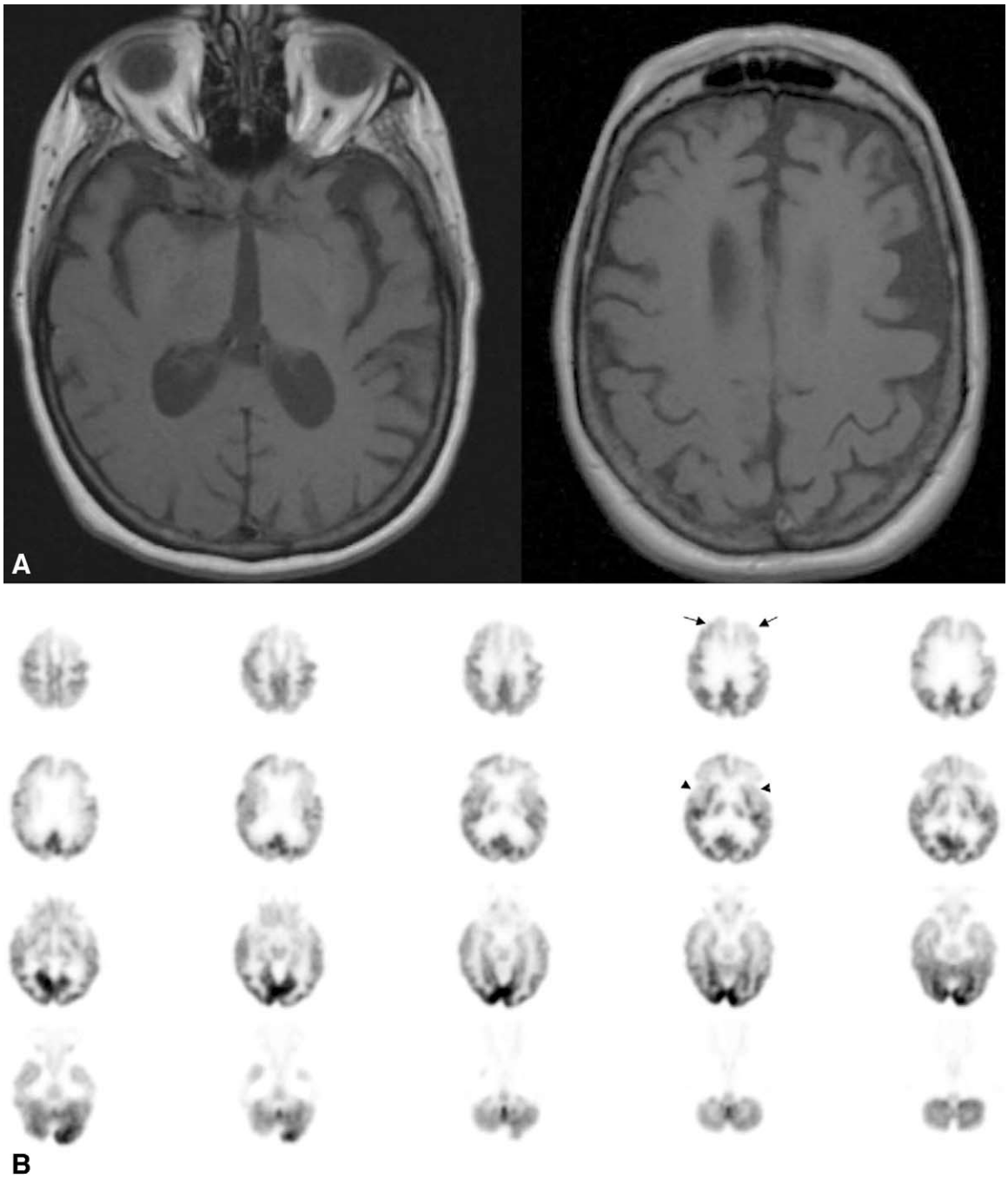

Figure 8 Frontotemporal dementia: A 62-year-old woman presenting with significant memory loss. (A) Magnetic resonance imaging performed 4 months before the PET study shows diffuse atrophy of the frontal and temporal lobes. (B-D) The positron emission tomography with 2-deoxy-fluorglucose (axial, coronal, and sagittal planes) scan shows significant hypometabolism in the frontal and temporal lobes bilaterally (arrows) with relatively preserved glucose metabolism in the parietal and occipital lobes.

ischemic in nature.[32,33] At present, the major indications for performing PET brain imaging are evaluation of transient ischemia, and determination of vascular reserve.[34,35]

Dementia

Since 1907, when Alois Alzheimer described the first case of severe and progressive dementia, Alzheimer's disease (AD) has been identified as a common form of dementia in the elderly.[36] At the present time, an estimated 4 to 5 million individuals are afflicted with the disease.[37,38] By they reach 85 years of age, more than 45% of the population are estimated to have AD. At present, the cost to care for these individuals is estimated to exceed $100 billion per year.[39,40] Even if the disease progression were delayed only for 5 to 7 years, an enormous societal benefit would be realized.

The standard workup of AD relies heavily on the clinical and neuropsychological evaluation. This approach uses standardized, well-validated testing and stringent NINCDS-ADRDA and DSM-

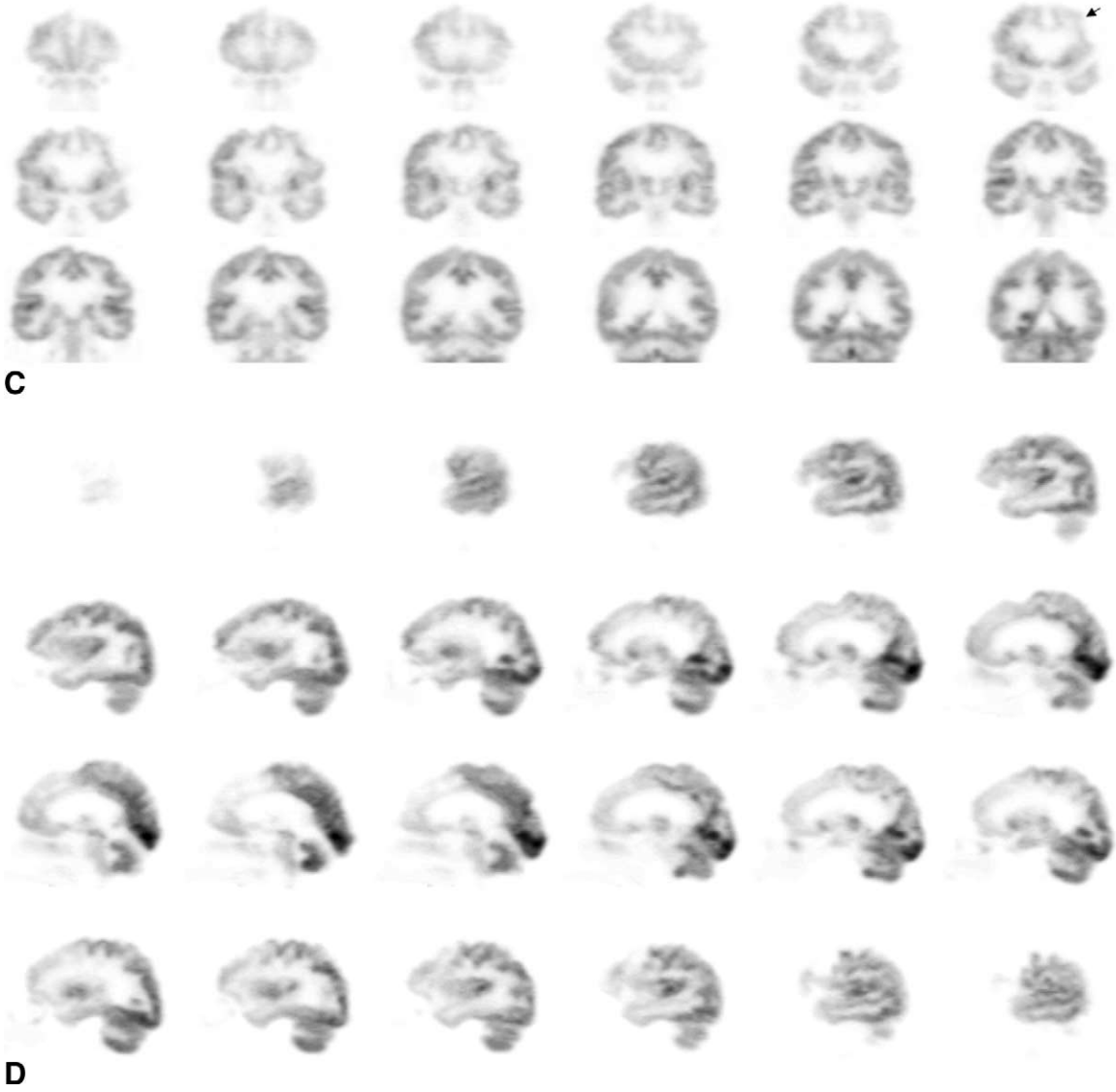

Figure 8 (continued).

III-R criteria.[41,42] In the best of circumstances, an accurate clinical diagnosis can be established in 70-90% of cases. The diagnosis, however, is much more difficult to establish very early in the evolution of the disease, at a time when appropriate treatment regimens would be more likely have the greatest impact on disease progression and quality of life.[43]

Recently, the standard workup of AD has been augmented by the use of PET imaging. The characteristic AD radiotracer distribution pattern for PET imaging has been well documented. In general, the radiotracer is diminished to varying degrees in the posterior parietal lobes, the temporal lobes and in some cases the frontal lobes. The primary neocortical regions, including the sensorimotor regions, the visual cortex and the subcortical gray matter are typically relatively well preserved. FDG cerebellar metabolic uptake, in general, is diminished relative to the cortex and subcortical gray matter (Fig. 5). However, in more advanced disease, the cerebellar metabolism tends to increase progressively, likely as part of a compensatory mechanism that involves recruitment of alternate neuronal pathways Fig. 6). In some patients, particularly early in the illness, the regional distribution of FDG may be quite asymmetric or even unilateral. This alteration in regional distribution of the radiotracer often correlates with neuropsychological testing particularly for patients with asymmetric patterns.[44-49] In general, the overall accuracy of FDG-PET imaging in detection of AD is superior to SPECT with sensitivities and specificities in the range of 87-94% and 85-96%, respectively.[39,50,51]

The clinical indications for performing PET (Table 2) in the assessment of dementia still are very much in evolution. PET imaging is a useful adjunctive technique in confirming the clinical diagnosis of probable AD and is even more useful in assessing patients with possible AD.[39,52] In the evaluation of the early stages of AD, PET is superior to SPECT. In addition, PET is useful in differentiating AD from other forms of dementia, including diffuse Lewy body disease; ischemic vascular dementia; frontotemporal dementia; Huntington's disease, Parkinson's disease; pseudodementia of depression and other forms of dementia, such as Creutzfeldt-Jakob disease and cognitive impairment secondary to substance abuse (Figs. 7 and 8).[53-55]

PET is an ideal imaging technique for the early detection of AD. PET can detect changes well before other current imaging modalities including CT, MRI, and SPECT imaging. The advan-

tages of early detection of AD include a significant reduction in the overall cost of establishing an accurate diagnosis of dementia; reduction in family member anxiety as the result of a prolonged time to establish a diagnosis; opportunity for the patient to direct care-related decisions while cognitive facilities are relatively intact; and the possibility of participating in emerging therapies at an early stage of the illness that might potentially delay clinical disability and improve overall quality of life.

The recent diagnostic imaging approaches have incorporated risk stratification techniques. A number of groups have combined information regarding genetic risk factors for AD with PET. Apolipoprotein (APOE), a gene on chromosome 19, has been reported to influence the risk of AD. The presence of the APOE-4 allele increases risk and decreases age of AD onset[56] whereas the APOE-2 allele appears to have a protective effect.[57] The presence of APOE-4 allele is, however, not sufficient to diagnose AD by itself.[58] Small and coworkers[59] and Reiman and coworkers[60] have reported that the combination of finding the presence of homozygous APOE 4 allele and an abnormal PET scan demonstrating bitemporal parietal hypometabolism is a very strong indicator for predicting that a patient will progress to AD. This diagnosis can be established at a time when patients are frequently asymptomatic and without findings on CT, MR, and neuropsychological testing.

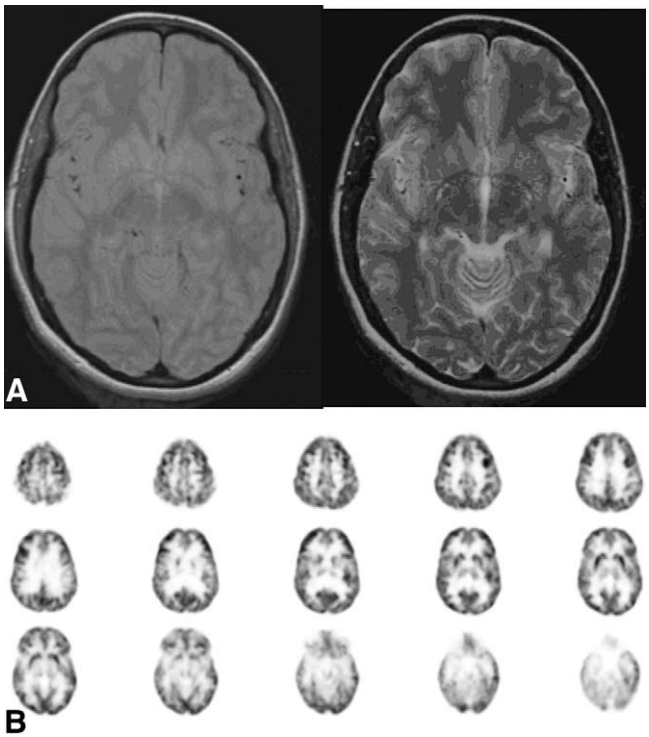

Figure 9 Complex partial seizure disorder: A 16-year-old girl presenting with a history of medically intractable partial complex seizures. Initial evaluation for possible surgical treatment consisted of magnetic resonance imaging (A) and EEG examination. Both of these studies were inconclusive for seizure foci. An interictal positron emission tomography with 2-deoxy-fluorglucose study (B) showed decreased glucose metabolism in the left posterior parietal region that was subsequently confirmed to be a seizure focus.

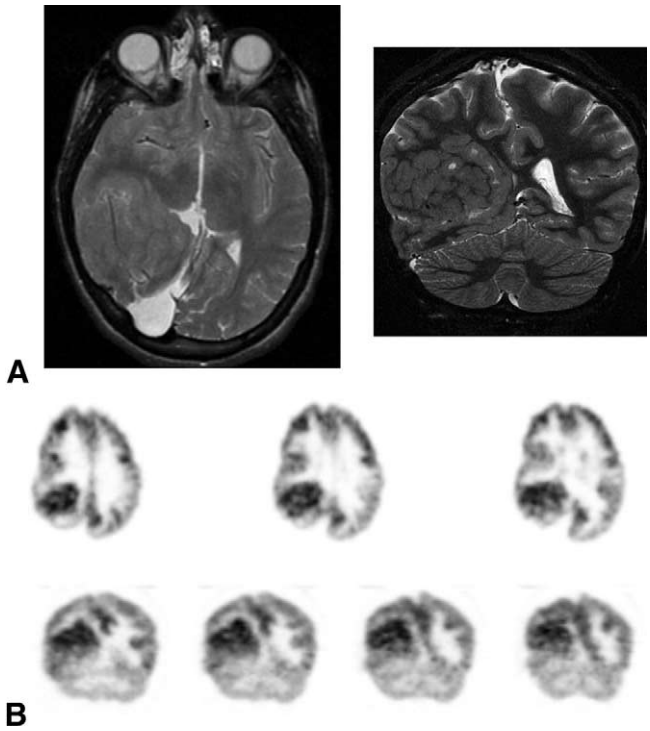

Figure 10 Complex partial seizures: A 14-year-old girl with an extensive migrational anomaly in the right temporal, parietal, and occipital lobes presents with medically refractory complex partial seizures. (A) Magnetic resonance imaging examination reveals a large right temporal, parietal occipital migrational anomaly. (B) Positron emission tomography with 2-deoxy-fluorglucose (axial plane, upper row; coronal plane, lower row) study demonstrates increased radiotracer activity in the region of the migrational anomaly consistent with subclinical seizure activity. Posterior to this region is a photopenic area corresponding to the large cerebrospinal fluid space seen on magnetic resonance imaging.

Epilepsy

The incidence of seizure disorders is quite significant. There are approximately 50,000 cases of medically intractable seizures in the United States of which approximately 500 cases undergo surgery each year.[61,62] Seizure disorders are generally classified either by symptoms or location. The most frequently used classification system was developed by the International League Against Epilepsy. Seizures are generally classified as generalized or partial.[63] The seizure disorder most commonly referred for medical imaging is the patient with a temporal lobe syndrome, typically complex partial seizures (CPS). The classic work up of a seizure disorder involves history and neurologic examination, video EEG monitoring; MRI and when necessary depth electrode EEG.[63]

Typically, adult-onset CPS will manifest evidence of medial sclerosis in the temporal lobe. This finding along with the appropriate clinical neurologic examination and video EEG pattern may be sufficient to establish a diagnosis and localize a surgical site in a patient who is medically intractable. However, in children and patients with a negative or equivocal workup, SPECT and PET imaging may play a crucial role.[63] PET imaging is typically performed interictally. The classic pattern in CPS is the visualization of a localized area of hypometabolism involving the temporal lobe. Interictal PET is reported to be significantly more

accurate than interictal SPECT with accuracy rates in the range of 65 to 79% versus 48 to 52% for SPECT (Fig. 9).[62,63] Ictal SPECT is, however, reported to be more accurate than interictal SPECT and PET with overall accuracy ranging from 89 to 94%.[61,64,65] The combination of interictal/ictal SPECT/PET has the highest overall accuracy rates. PET imaging has also been shown to of value in the assessment of extratemporal seizure foci (Fig. 10).

Head Trauma

Several hundred thousand individuals in the United States experience some form of head trauma each year. The consequences of head trauma range from the very severe, resulting in a vegetative state or death, to the very mild, resulting in complete recovery. Of particular interest is a subset of symptomatic patients well past the acute stage whose CT and MRI reveal no structural abnormalities.

In evaluating acute head injury, CT and MR are the primary diagnostic tools. They play a critical role in detecting intracranial lesions that may require neurosurgical intervention. It should be noted, however, that SPECT and PET brain imaging have been found to be better than CT or MRI as prognostic indicators and thus may play a valuable role in the critical care management of these patients. In general, patients with larger and or more numerous lesions encountered on SPECT or PET relative to CT or MRI tend to have a poorer prognosis and conversely an initial negative SPECT has been found to correlate with an excellent prognosis.[66-69]

During the chronic stage, the usefulness of CT and MRI brain imaging is more limited. Both PET and SPECT brain imaging have been shown to detect a greater number of lesions after head trauma than CT and MR. This is particularly the case after mild-to-moderate head trauma, including patients who did not experience loss of consciousness. Thus, PET or SPECT brain imaging have been advocated for use in patients with negative CT and/or MRI but persistent (3-6 months) behavior, cognitive, or psychiatric symptoms after head trauma. These patients most typically are individuals with mild head trauma and postconcussive symptoms.[70]

The relationship of SPECT findings after brain trauma and neuropsychologic testing are currently under investigation. Preliminary studies appear to indicate that abnormalities in neuropsychologic testing have a corresponding correlate on SPECT, but SPECT findings do not necessarily have neuropsychologic correlates.[56] These results are similar to those observed with MRI whereby structural abnormalities detected on MRI do not always have neuropsychologic correlates.[66] There are several possibilities that may account for this discrepancy including the hypothesis that specific lesions in the brain may be not be accompanied by signs or symptoms due to either a lack of an appropriate critical tissue mass or to compensation from other parts of the brain.

SPECT and PET studies that are taken after head trauma may demonstrate different patterns of involvement depending on the severity and type of injury, that is, motor vehicle, blunt trauma, or fall.[2] One pattern that is rather specific for brain trauma consists of focal well-circumscribed area(s) of decreased perfusion (one or more sites). Other less-specific patterns can also be seen. Thus, brain perfusion studies after brain injury can mimic other disease states and therefore the interpretation of a SPECT or PET brain scan in patients who sustain head trauma must be carefully correlated with history and clinical findings.

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