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Assessment: Positron emission tomography

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

This technology assessment paper on positron emission tomography (PET) was produced by a panel of experts in the field who were asked to evaluate the safety and clinical efficacy of PET on the basis of the current scientific and clinical information available in the literature. Opinions were also solicited from the Academy membership at large. Since such literature is subject to inconsistencies in subject selection, methodology, and sample size, the assessment paper should be considered complementary to but not a substitute for a comprehensive prospective assessment of the clinical efficacy of the technique.[1-4] A prospective study is currently underway to evaluate physician decision making based on PET data. The assessment paper, thus, represents a synthesis of the literature and expert opinions and is intended to reflect state of the art knowledge concerning PET as a technology. The statements in the assessment paper should be reconsidered as new information becomes available. We have provided the associated opinions as a guide to the Academy membership until a more rigorous scientific assessment becomes available.

The PET method. PET is a technique that utilizes positron-emitting radiopharmaceuticals to map the physiology, biochemistry, hemodynamics, and pharmacology of the human body.[5,6] Positron-emitting radioisotopes produced in a medical cyclotron are incorporated into compounds that are biologically active in the body. A positron emission tomograph provides cross-sectional images of the distribution of these radiolabeled compounds in the body. The data obtained can be used as a quantifiable map that describes the metabolic, biochemical, or pharmacologic process of interest when used with an appropriate mathematical model.

PET is capable of performing many biochemical assays and measurements that vary with the positron-labeled tracer. Each will have to be tested in a research setting for safety and clinical efficacy prior to clinical use. Each use should be reviewed independently as it is introduced.

Most clinical applications in the nervous system have employed the use of ^{18}F-fluoro-2-deoxy-D-glucose (FDG) for the measurement of local cerebral glucose metabolism. The 12 years of experience with FDG was, in turn, based on 10 years of prior experience with ^{14}C-2-deoxyglucose in laboratory studies.[7] Oxygen-15 labeled water, carbon dioxide, carbon monoxide, and oxygen gas have been used in nuclear medicine for decades and in conjunction with PET since the 1970s[8] to measure cerebral blood flow, blood volume, and oxygen utilization. A wide range of labeled substrates, substrate analogs, drugs, ligands, and other biochemically active compounds have been developed and are in the process of clinical evaluation.

For example, ^{18}F-L-dopa has been employed to evaluate presynaptic dopamine terminals, while various ^{11}C- and ^{18}F-labeled analogs of spiperone and raclopride have been used to examine postsynaptic dopamine receptors. These compounds have promising and potentially important clinical applications in neurology, but neither is currently in clinical use.

Because PET has been slow in entering the clinical arena, an extensive literature has accumulated defining the clinical utility of PET in the diagnosis of cerebral disorders. In addition, a broad database has been obtained in normal subjects, which is the proper prerequisite for applying any technique to diagnostic decisions. Because the information obtained with PET is biochemical in nature, it typically will show abnormalities prior to any change in the anatomy of the brain that might be identified with CT or MRI. While both EEG and PET provide functional information, they are complementary rather than redundant. This is true because EEG provides information about the synchrony of electrophysiologic events occurring at the surface of the brain in close proximity to the electrodes. PET, on the other hand, provides measures of metabolism and substrate utilization in relatively large volumes (0.25 ml) of tissue in 3 dimensions, throughout the complete volume of the brain.

There are currently 28 PET centers (34 PET scanners) in North America, with an additional 14 to open shortly. Thus, PET is neither new nor limited to university sites. Thousands of PET examinations have been performed in the United States and Canada.

Safety. PET employing FDG or ^{15}O-labeled compounds is a safe procedure. Studies, carried out over a period of the last 13 years, have all been performed without any significant adverse events. The majority of

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the patients evaluated with PET have been studied using research protocols, but as an ever increasing number of clinical PET centers open, the ratio of research to clinical cases is falling. Radiation exposure in a typical PET procedure results in an absorbed dose that is less than or equal to that received in many other routine radiodiagnostic medical procedures.[9,10]

In research studies, protocols typically require placement of an intra-arterial or venous catheter for blood sampling to monitor the plasma concentrations of the radioisotope following its administration. These procedures are not typically applied to clinical studies where adequate information can be achieved without blood sampling. As with other imaging techniques, the patient must remain quiet and still during the examination. For the great majority of subjects this has not proved to be a problem.

Clinical utility. This section describes the clinical areas where PET studies can be recommended as clinically safe and useful in the evaluation of neurologic disease. As noted below, the patterns of metabolism or blood flow seen in PET images of these conditions may not be specific for an individual disease entity. Nevertheless, when taken in the proper clinical setting, these studies provide unique and previously unobtainable information, the pattern of which provides specific diagnostic data for the patient and physician. Among the indications for the clinical use of PET are the following:

Presurgical evaluation of patients with refractory seizure disorders. Patients with uncontrolled seizures of presumed focal origin who are candidates for epilepsy surgery may benefit from interictal FDG-PET scans. Both pediatric and adult patient populations have been studied, and more than 10 years of experience have accumulated. PET must be placed in the context of the range of tests used to evaluate patients for possible surgery, including neurologic examination, routine EEG, MRI and CT, neuropsychological tests, intensive video-EEG monitoring (usually with drug withdrawal in order to obtain ictal records), and invasive studies using depth electrodes or subdural strips and grids.[11-14] The use of FDG-PET complements these evaluations and obviates the need for invasive evaluation in selected cases.

The detection of unilateral temporal hypometabolism ipsilateral to the EEG focus, found in as many as 75% of patients with complex partial seizures (CPS), is a highly specific and valuable procedure for the localization of the seizure focus.[15-17] In this patient group, PET is more sensitive than MRI or CT.[13,14,18,19] Interictal focal hypometabolism is present in a smaller proportion of patients with CPS of extratemporal origin.[20] In conjunction with neuropsychological tests, PET is used to assess possible adverse cognitive effects of surgery by revealing the presence of bilateral or multifocal hypometabolism. The presence of widespread hypometabolism with PET in a patient with apparently well-localized EEG discharges suggests more diffuse cerebral dysfunction, and may indicate that the chance of surgical success is limited.

In patients with intractable CPS where PET shows focal hypometabolism, and EEG findings plus selected other noninvasive tests indicate a unique site for seizure origin (30% to 40% of cases), invasive electrophysiologic monitoring can be eliminated. This increases safety and reduces total cost by a substantial amount (ie, in many centers this currently amounts to a $15,000 to $20,000 savings).[11]

Although it is not yet established that focal hypometabolism in PET scans is a valid indication for surgery in a patient with nonlocalized surface EEG seizure origin, the PET findings will help to plan and reduce the scope of invasive electrode evaluation, allowing the use of unilateral subdural arrays rather than more invasive bilateral depth electrodes.[21]

Studies indicate that a proportion of children with uncontrolled neonatal seizures and infantile spasms may have focal PET hypometabolism even when all other studies are nonlocalizing, thus allowing surgery to be performed in a group of patients for whom no other effective therapy exists.[22]

Uncontrolled epilepsy is an important medical and social problem. PET contributes to its solution by increasing the number of patients who can be treated surgically, helping to plan the surgical approach in a safer and more cost-effective manner, and, in some cases, suggesting that surgery might be inappropriate.

Cognitive decline and differential diagnosis of dementia. PET with FDG or oxygen 15 labeled compounds aids in the early differential diagnosis of dementia.[23,24] Patients with cognitive complaints due to Alzheimer's disease, Parkinson's disease, Huntington's disease, progressive supranuclear palsy, olivopontocerebellar atrophy, and multi-infarct dementia have distinct patterns of abnormal cerebral metabolism that can be demonstrated with PET.[17,25-38] Such patients typically have normal structural imaging studies early in their course and nonspecific changes in later stages of disease.[39] In contrast, the metabolic patterns found in normal aging are similar to those of normal young adults.[17,26,29,40] PET cerebral glucose metabolism studies can differentiate between these dementing disorders, providing information that is complementary to more conventional diagnostic methods. For example, Alzheimer's disease typically causes bilateral superior parietal hypometabolism that extends into the inferior parietal and temporal lobes with disease progression.[23,27,28,35,41] On the other hand, multi-infarct dementia, which can be mistaken clinically for Alzheimer's disease, causes multiple asymmetric regions of cortical and subcortical hypometabolism.[38] The FDG-PET studies additionally demonstrate characteristically abnormal patterns in progressive supranuclear palsy and in Huntington's disease at times when conventional neuroimaging studies are normal.[30,42]

PET studies can result in an earlier and more specific diagnosis of dementia and obviate the need for repeated laboratory and structural imaging techniques (eg, EEG, CT, and MRI) in which the typical expectation on the part of the clinician is to find a normal study or, in rare instances, a finding such as a brain tumor or a subdural hematoma. By providing a definitive diagnosis, PET studies further reduce the ambiguity and anguish asso-

ciated with a less specific diagnostic outcome as well as the expense of other lower-yield diagnostic procedures. It is anticipated that the introduction of clinical PET will result in its being the most definitive test used in the diagnosis of patients with dementia.

Movement disorders. PET is useful in distinguishing some movement disorders that are otherwise difficult to differentiate. Parkinson's disease with dementia is frequently confused with progressive supranuclear palsy on the basis of clinical examination alone, yet PET with FDG demonstrates different patterns of hypometabolism in each disorder. Progressive supranuclear palsy causes predominantly frontal hypometabolism while Parkinson's disease with dementia in many patients causes bilateral temporoparietal hypometabolism. Similarly, progressive supranuclear palsy can be confused clinically with olivopontocerebellar atrophy early in the course. PET with FDG may be useful in distinguishing these 2 conditions since the latter is associated with cerebellar and brainstem hypometabolism for glucose.[30,34,43,44]

The detection of caudate hypometabolism in the absence of caudate atrophy in patients with a positive family history and with symptoms of early Huntington's disease provides useful confirmatory evidence, giving added support for this diagnosis.[42,45-47] Similarly, in patients with typical clinical features but an unclear family history, the presence of caudate hypometabolism supports a diagnosis of Huntington's disease. These observations must be interpreted with caution, however, and in conjunction with the clinical findings, as these changes are not specific for Huntington's disease. Similar metabolic abnormalities have been described in chorea-acanthocytosis, benign hereditary chorea, and Lesch-Nyhan disease.[48-50] PET may ultimately prove useful in the investigation of presymptomatic Huntington's disease, but at present this should be considered investigational.[51-53]

Brain tumors. Cerebral glucose metabolic studies are extremely useful in the management of brain neoplasms. Work in this area has been ongoing for 10 years and identifies clinical utility for PET in 2 settings. First, PET studies are useful in the grading of tumor malignancy and in presurgical planning for biopsies. Local cerebral metabolic rates for glucose correlate with the degree of malignancy in gliomas and can differentiate low-grade (I and II) from high-grade (III and IV) gliomas.[54-57] Similarly, although less thoroughly studied, glucose metabolism parallels tumor growth patterns of meningiomas and assists in predicting postsurgical recurrence of these tumors.[58] Therefore, PET with FDG may be used to direct stereotactic biopsies of unresectable gliomatous lesions and to estimate the grade of malignancy prior to biopsy or resection. In addition, PET identifies the site of the most highly metabolic regions, which are likely to contain the tumor of the highest grade, and avoids regions of tumor necrosis, which provide little diagnostic information. The result is enhanced diagnostic yield of biopsies and more appropriate planning of subsequent therapy.

The 2nd use of PET with FDG is in the differentiation of recurrent high-grade tumors from radiation- or chemotherapy-induced necrosis.[59-62] These entities have similar appearances and are essentially indistinguishable on structural brain imaging studies. On PET, recurrent tumors are hypermetabolic in their appearance while radiation necrosis has little or no metabolic activity. Most patients have mixtures of necrosis and tumor. Noninvasive recognition of pure necrosis by PET avoids the disastrous possibility of giving additional radiation or chemotherapy to the patient with ambiguous CT or MRI findings. Conversely, in patients with specific areas of residual viable tumor, PET can be used to plan and direct the intended surgery. Thus, PET provides key information and is, in fact, the only method capable of distinguishing necrosis from tumor. All these features reduce risk to the patient as well as cost.

Promising clinical applications. An extensive literature exists on the use of PET in various forms of cerebrovascular disease.[63-66] A variety of interesting observations have been made in patients with transient ischemic attacks, acute stroke, and subarachnoid hemorrhage using measurements of local blood flow, blood volume, oxygen consumption, and glucose metabolism. Some of these observations have correlated with experimental observations in animals, and have provided in vivo measurements in humans of sequential changes in flow and metabolism in acute stroke. We have greatly expanded our understanding of the effect of large-vessel occlusion on the hemodynamic and metabolic status of uninfarcted brain tissue distal to such an occlusion. Studies in the newborn have revealed new relationships between brain blood flow and oxygen consumption that appear unique to the newborn state. Despite these important observations, PET has not yet established a role in the clinical management of patients with cerebrovascular disease. Only further study based upon these important beginnings will establish whether PET will have a role to play in the clinical management of patients with cerebrovascular disease.

While there are insufficient data to recommend their clinical use, other promising applications for PET exist and have been described in the literature. In addition to the use of tracers to measure metabolism and blood flow, presynaptic (eg, labeled L-dopa) and postsynaptic (eg, labeled analogs of spiperone and raclopride) tracers have been used to study movement disorders (eg, to differentiate parkinsonian syndromes) and to evaluate psychiatric and neurobehavioral disorders. Cerebral metabolism has been measured in vegetative states versus locked-in syndromes[67] and may prove useful in evaluating brain death. The role of PET in the evaluation of head trauma has not currently been established.

In addition to the indications for clinical PET imaging of metabolism with FDG that have been described in this assessment paper, it is clear that additional clinical applications for PET will be forthcoming in the near future. Many hundreds of positron-labeled tracers for PET are in development or under research investigation at the present time. These are likely to provide insights into biochemical changes in the brain that cannot otherwise be recognized during life. The

ability to view such pathophysiologic alterations in brain biochemistry will undoubtedly have significant diagnostic importance.

Executive summary. PET with FDG or ^{15}O-labeled compounds is a safe and efficacious diagnostic clinical technique. It is, at the least, complementary to, and often unique rather than redundant with, structural imaging and EEG. PET has clinical efficacy in the areas of localization of seizure foci in patients with refractory seizure disorders who are candidates for epilepsy surgery, in the differential diagnosis of dementia and movement disorders, in the grading of primary brain tumors, in the localization of brain tumor biopsy sites, and in the differentiation of recurrent high-grade gliomas from radiation-induced brain necrosis. The application of PET provides previously unavailable information about these disease categories that should lead to a reduction in patient morbidity, mortality, and cost.

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