PET Imaging for Traumatic Brain Injury

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KEYWORDS

• Traumatic brain injury • Diffuse axonal injury
• PET • Fluorodeoxyglucose

With over 1.5 million annual incidences resulting in an estimated 50,000 deaths, 300,000 hospitalizations, 80,000 to 90,000 long-term disabled individuals and estimated costs at greater than $60 billion, traumatic brain injury (TBI) represents a major health problem in the United States.[1–3] Neuroimaging is critical for timely, accurate diagnosis and optimal management of the TBI patient. Although plain radiographs, magnetic resonance imaging (MRI), single photon emission computed tomography (SPECT) and PET all have been employed, computed tomography (CT) represents the principal imaging modality for TBI. This likely will and should continue because of CT's exceptional ability to demonstrate skull fractures, epidural hematomas, subdural hematomas, and other acute pathologies associated with TBI that require expedited management decisions.[3–7]

Once outside of the critical management window, the additional afore-mentioned neuroimaging modalities may be of value. Because the arsenal remains limited to treat TBI and the understanding of TBI pathophysiology also remains primitive, in vivo central nervous system (CNS) imaging advances will continue to shape patient management. Specifically, because the basis of PET imaging is underlying cellular molecular biologic change, it has the potential to provide unique insights into this disease and its treatment. This article will examine the body of PET imaging focused upon traumatic brain injury and contemplate PET's role in future experimental and, possibly, clinical practice.

FLUORODEOXYGLUCOSE AND PET

The most prominent contemporary role in medicine of PET is revealing the locations of glucose hypermetabolism indicative of neoplastic disease.[8,9] By superimposing function on anatomy, PET/CT has shown superiority compared with PET alone in cancer mapping, and that is why combination machines are rapidly replacing PET-only ones.[9–14] Before the existence, availability, and popularity of functional MRI (fMRI), it is important to note that PET first was used to visualize in vivo human brain function.[15,16]

The radiotracer ^{18}F-fluorodeoxyglucose (^{18}F-FDG) usually is inferred when PET imaging is mentioned. It is a glucose analog, and, within mitochondria, metabolized by hexokinase to ^{18}F-FDG-6-phosphate rather than 2-deoxy-D-glucose, whereby it becomes trapped and continues to emit a positron.[17] Not surprisingly, the more severe the head injury, the more likely a reduction in brain glucose metabolism will be detected.[18,19] As in the case of stroke, Alzheimer's-type dementia and Pick's disease, FDG-PET demonstration of focal metabolic defects often correlate with specific functional deficits endured by TBI patients (**Fig. 1**).

FDG-PET also can detect abnormalities in TBI patients when they are absent on MRI and CT.[20–23] Some studies have revealed that as much as 42% of PET abnormalities were not associated with any lesions observed on anatomic images.[24,25] Lesions such as cortical contusions, intracranial hematomas, and subsequent encephalomalacias

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usually are confined to the site of injury, while subdural and epidural hematomas often cause widespread hypometabolism and even may affect the contralateral hemisphere.[24,25] Diffuse axonal injury has been found to cause diffuse cortical hypometabolism and a marked decrease in parieto–occipital cortical metabolism.[24–26] An example of this finding is illustrated in **Fig. 2**. Lupi and colleagues also noted a pattern of relatively increased metabolism of the cerebellar vermis in 54 of 57 TBI patients.[27] **Fig. 3** demonstrates such an example.

FDG-PET also has been of great value in revealing seizure foci.[28–32] Specifically, epileptogenic foci are thought to be hypometabolic during interictal status and reflected by a decrease in radiotracer distribution.[30,32] FDG-PET therefore, has been used to identify such regions in mesial temporal lobe epilepsy and types of focal cortical dysplasias.[29,31] Ferguson recently published a retrospective analysis of TBI patients and their respective risk of developing post-traumatic encephalopathy (PTE) and found an incremental risk corresponding to severity of injury.[33] Within 3 years after being discharged, patients with mild, moderate, and severe TBIs had an incidence of developing epilepsy of 4.4, 7.6, and 13.6 per 100 persons, respectively.[33] FDG-PET even has been used to help guide whether a combat pilot could return to duty after a TBI.[34]

PET: ^{15}O

Although PET imaging usually is assumed to map glucose metabolism, there are several other tracers that have been employed to study TBI. Even though it requires a cyclotron facility on premises because of its short half-life, positron-labeled oxygen (^{15}O water) has been used successfully in several PET TBI studies.[35–46] Because of its short 2-minute half-life, any ^{15}O injection and consequent imaging are technically demanding and also require some time for preparation. This complexity is amplified in the clinical setting of a TBI patient, especially one in critical status, making it very impractical.

Despite the challenge of using such a short-lived isotope, ^{15}O has been used to examine the role of hypoxia in TBI because of the ischemic cell damage that occurs in 90% of these patients. This ischemia likely is mediated by the release of various toxins in response to the molecular events associated with brain injury, which, in turn, also may lead to an ischemia–reperfusion injury.[47,48]

Such ^{15}O studies have demonstrated increased oxygen extraction fraction in regions of brain with reduced cerebral blood flow[40,45]; however, such oxygen delivery within hypoxic brain may not achieve normal diffusion rates.[41] These studies also have attempted to establish an ischemic burden of injury in the TBI patient.[37,38] For example, Cunningham and colleagues[38] demonstrated that although cerebral oxygen use in the TBI patient is comparable with that observed in stroke patients, cerebral blood flow thresholds are inherently different between the two patient populations. The heterogeneity of TBIs only further complicates the comprehension of its pathophysiology.

Although ^{15}O PET imaging may offer a global map of brain oxygenation in the traumatic brain injured patient, it represents but a small period of time. Therefore, ^{15}O PET imaging also has been correlated with more invasive, localized, and dynamic measurements of brain oxygen content,

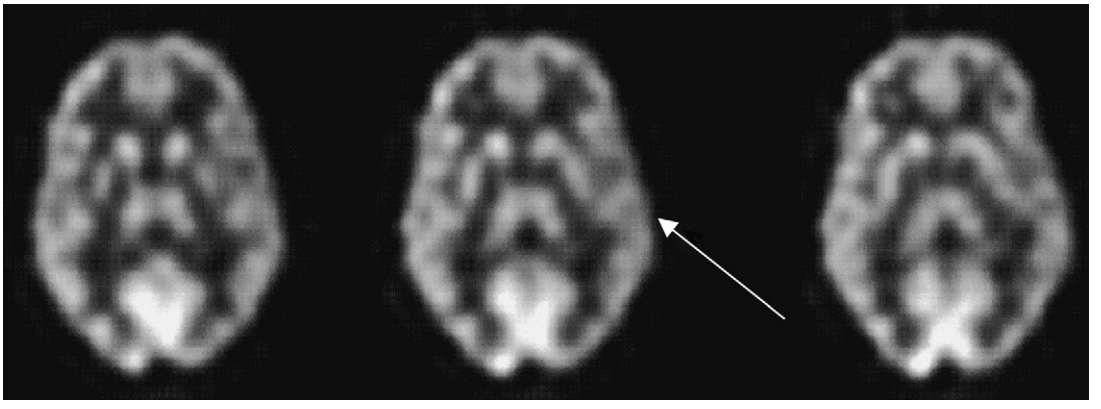

Fig. 1. FDG-PET scan of a 43-year old woman who suffered a head injury 2 years before this study and now has cognitive and memory dysfunction and language problems. This scan demonstrates hypometabolism of the entire left hemisphere *(arrow)* relative to the right. *Abbreviation:* FDG-PET, fluorodeoxyglucose–PET.