Technetium-99m-HMPAO SPECT in the Evaluation of Patients with a Remote History of Traumatic Brain Injury: A Comparison with X-Ray Computed Tomography

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The functional imaging modality has potential for demonstrating parenchymal abnormalities not detectable by traditional morphological imaging. Fifty-three patients with a remote history of traumatic brain injury (TBI) were studied with SPECT using ^{99m}Tc-hexamethylpropyleneamineoxime (HMPAO) and x-ray computed tomography (CT). Overall, 42 patients (80%) showed regional cerebral blood flow (rCBF) deficits by HMPAO SPECT, whereas 29 patients (55%) showed morphological abnormalities by CT. Out of 20 patients with minor head injury, 12 patients (60%) showed rCBF deficits and 5 patients (25%) showed CT abnormalities. Of 33 patients with major head injury, 30 patients (90%) showed rCBF deficits and 24 patients (72%) showed CT abnormalities. Thus, HMPAO SPECT was more sensitive than CT in detecting abnormalities in patients with a history of TBI, particularly in the minor head injury group. In the major head injury group, three patients showed localized cortical atrophy by CT and normal rCBF by HMPAO SPECT. In the evaluation of TBI patients, HMPAO SPECT is a useful technique to demonstrate regional brain dysfunction in the presence of morphological integrity as assessed by CT.

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Head trauma is a leading cause of morbidity and mortality among accident victims and its accurate diagnosis remains one of the most interesting and challenging areas of medical imaging today. True epidemiological data on traumatic brain injury (TBI) is difficult to obtain due to under-reporting of minor injuries and deaths prior to reaching the hospital. Varying definitions regarding the extent of injuries have lead to additional inaccuracies. Nevertheless, some studies have estimated the overall incidence of TBI to be approximately 200/100,000 (*1–3*). This figure is similar to that for stroke, and greater than that for epilepsy (*1*). While the epidemic proportions justifiably raise concern, the morbidity and mortality data are alarming. The mortality associated with TBI ranges from 34% to 49%, with particularly high rates of death occurring in the first 48 hr post-trauma (*4*). The morbidity from TBI is also significant. Victims suffer from prolonged periods of physical, neurological and neuropsychological incapacitation often with associated social and occupational dysfunction. Thus, TBI represents a tremendous burden on society in general, and the health care sector in particular. Proper management of these surviving victims is essential and requires an understanding of the pathophysiology of TBI as well as accurate diagnosis, assessment, and prognostication of the post-TBI patient status.

In an effort to understand the mechanism contributing to the prolonged morbidity in these patients, various anatomical imaging modalities [x-ray computed tomography (CT) and magnetic resonance imaging (MRI)] together with neuropsychological testing have been employed (*5–18*). Recently functional imaging has also been added to the armamentarium for assessing TBI patients. Most studies employing functional imaging have used positron emission tomography (PET) imaging (*10,19–24*). These studies have furnished additional information to the structural/anatomical information derived from CT and MRI. For example, it has been shown that the perfusion deficit in a patient may extend beyond the structural abnormality detected on CT or MRI (*19,20,23*) and that diffuse axonal injury secondary to trauma can result in widespread hypoperfusion (*20*). However, PET is an expensive and complex imaging modality and as such is limited in its general clinical application.

An alternative method of functional imaging combines the use of single-photon emission computerized tomography (SPECT) with the regional cerebral blow (rCBF) agent ^{99m}Tc-hexamethylpropyleneamineoxime (HMPAO). At present, the SPECT literature on TBI (*25–30*) is even more limited than that of PET. Two of these studies dealt with the role of this imaging modality in the acute setting

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(*25,27*). The other studies, all preliminary communications (*26,28–30*), are the only studies to date where HMPAO SPECT has been employed to assess individuals who have experienced a TBI in the remote past. These studies have shown this imaging modality to be sensitive in detecting functional abnormalities of the brain.

In the present study, HMPAO SPECT imaging was compared with CT in a population of patients with a remote history of a TBI, the working hypothesis being that the functional imaging modality can demonstrate parenchymal abnormalities not detectable by traditional morphological imaging. Preliminary work for this study has been presented previously (*30*).

MATERIALS AND METHODS

Subject Selection

Patients were recruited from the rehabilitation medicine practice of W.F. Only those patients with a history of a TBI which had occurred at least 6 mo earlier were studied. Patients were excluded from the study if they: (1) had previous TBI (i.e., had more than one TBI), (2) had previous intracerebral insult other than TBI (i.e., abscess or infarct), (3) had a history of neuropsychiatric problems antedating TBI, (4) had history of drug or alcohol abuse, (5) were less than 10 yr of age at the time of trauma, and (6) were greater than 50 yr of age at the time of imaging.

Patients were classified into two groups as outlined in Table 1. These criteria fit those patients at either end of a spectrum of severity, with the intermediate group (i.e., those patients with a Glasgow Coma Scale (GCS) of 9–12) not represented (*31–35*).

Fourteen normal control (NC) subjects (all right-handed, 7 males and 7 females, age range 25–48 yr with a mean of 32 yr) were also selected for HMPAO SPECT imaging. They were screened according to the above exclusion criteria together with an additional criteria of no history of a TBI. The NC project was granted ethical approval by the Human Subjects Review Committee of the University of Toronto.

HMPAO SPECT Imaging

After informed consent was obtained, each subject underwent HMPAO SPECT imaging as outlined below. Prior to administration of the radiopharmaceutical, subjects were given 500 mg of potassium perchlorate orally in order to reduce the amount of uptake by the parotid gland. HMPAO (Ceretec, Amersham) was prepared according to the manufacturers instructions, and within 30 min, 20 mCi (740 MBq) of the radiopharmaceutical were injected intravenously in a quiet room with the subject's eyes open. Ten to 15 min later, subjects were imaged in the supine position with their heads secured in a specially designed adjustable head holder. SPECT imaging was performed using a truncated head rotating gamma camera (Elscint 409 AG) interfaced to a dedicated computer (Elscint PS1). At the starting position (0 degrees), the camera face was perpendicular to the subject's orbital-meatal line. A total of sixty 25-sec images were obtained through a 360-degree circular revolution (step-and-shoot paradigm), using a high-resolution parallel-hole collimator. The average radius of rotation was 12 cm. The resolution of the system, expressed as full width at half maximum at the center of the field of view and at a depth of 12 cm from the camera face, was 14 mm. In 25 min, a total of 2.5–6.0 million total counts were collected. The data, which were acquired in word mode on a 64 × 64 matrix, then were normalized to byte mode and corrected for nonuniformity according to Elscint specifications. One-pixel (7 mm) thick transaxial slices were reconstructed, parallel to the orbital-meatal line using a modified Hanning back projection filter. A magnification zoom of 1.8 was used during the reconstruction. The first-order Chang method of attenuation correction was employed (*36*). Transaxial data then were reoriented and reconstructed in 1-pixel thick coronal and sagittal slices. Each set of transaxial, sagittal and coronal images were normalized to the maximal pixel count in the respective set and recorded on film with a lower count density threshold of 30% on a continuous 256 grey scale for visual assessment.

TABLE 1
Classification of TBI Patients Based on the Severity of Their Injury

Minor Head Injury
1. Brief loss of consciousness (LOC) ≤20 min.
2. Glasgow Coma Scale (GCS) 13–15.
3. Brief hospitalization of 2 days or less.

Major Head Injury
1. Coma (GSC ≤ 8) for 1 hr or more.
2. Post-traumatic amnesia (PTA)* of 24 hr or more.

* PTA = the elapsed time between the injury and the restoration of continuous ongoing memory.

X-ray CT Imaging

All patients had at least one CT of the head at a time interval of 6 mo or greater after TBI. Such scans consisted of 10-mm contiguous transaxial slices from the base of the skull to the vertex without the administration of intravenous contrast material. Some patients also had additional CT scans at the time of their injury, thereby allowing for comparative assessment of changes over time.

Data Analysis

All HMPAO SPECT images were assessed for technical adequacy. The rCBF was analyzed and categorized as normal, decreased or increased, and with focal or diffuse involvement. Identified perfusion deficits were then localized to a specific anatomical region of the brain and visually quantified on a scale of 1 to 3, corresponding to mild, moderate, and severe.

All CT scans were independently reviewed and regions of focal or diffuse brain parenchymal abnormalities localized in a manner similar to that for HMPAO SPECT images.

Interpretation of HMPAO SPECT and CT images was performed independently. In addition, no specific clinical information (i.e., mechanism or severity of injury, symptomatology) was available at the time of assessment except for the knowledge that the patient had sustained a TBI.

The results from the two imaging modalities were then compared to see if there was any degree of concordance in the abnormal findings. For this purpose, the patients were classified into three groups as follows: complete concordance (both the location and severity of the defects were judged to be the same), partial concordance (some of the defects were matched but in addition either or both imaging modalities showed unmatched findings as well) and no concordance (no matched findings seen).

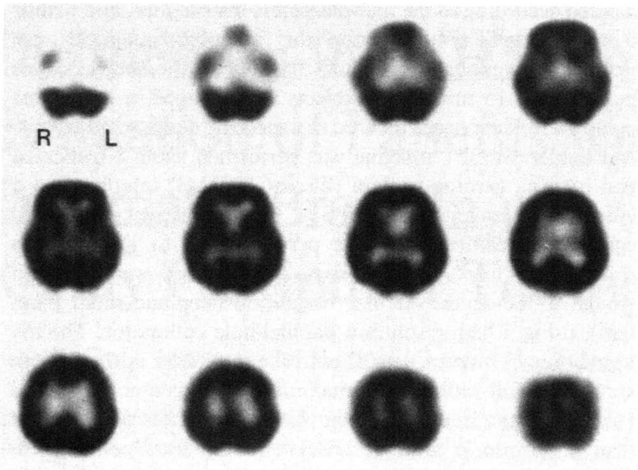

FIGURE 1. Transaxial HMPAO SPECT images from a 41-yr-old normal control subject.

RESULTS

Of a total of 156 TBI patients who were referred for HMPAO SPECT imaging, only 111 patients met the study criteria. Of this latter group, only 53 patients had a CT at an interval greater than 6 mo after the traumatic event (20 of these patients also had a CT closer to the time of the traumatic event). Twenty patients were classified as having suffered from a minor head injury, while 33 patients were classified into the major head injury group.

All HMPAO SPECT studies were visually judged to be technically adequate. The NC group showed homogeneous and symmetrical distribution of the radiopharmaceutical activity throughout the grey matter with greater activity in the region of the cerebellum followed by the medial occipital lobes. Basal ganglia activity equalled the cerebral cortical activity (Fig. 1).

In the TBI patient group, there was no abnormally increased rCBF. Instead, either well-defined focal and/or diffuse rCBF deficits were identified. Overall, 42 patients (80%) showed rCBF deficits by HMPAO SPECT, and 29 patients (55%) showed morphological abnormalities by CT. Table 2 further divides the patients into minor and major head injury groups to determine the frequency of identified abnormalities with each imaging modality. The difference between the two imaging modalities appears more accentuated for the minor TBI group. However, Table 2 only reflects the presence or absence of an abnormality and does not include certain aspects of partial concordance (i.e., where both modalities show an abnormality, yet the functional deficit may exceed the morphological abnormality). Table 3 summarizes for both the minor and major TBI patient groups the degree of concordance of the HMPAO SPECT and CT findings. It can be seen that partial concordance plays a more significant role in the major TBI group. The degree of concordance (complete or partial) between the HMPAO SPECT and CT findings for the minor TBI group was 11/20 (55%), whereas it was 27/30 (82%) for the major TBI group.

TABLE 2
Comparison of the Frequency of Visually Detected Abnormalities with HMPAO SPECT Versus CT for the Two Patient Groups

	HMPAO SPECT	CT
Minor (n = 20)	60%	25%
Major (n = 33)	90%	72%

TABLE 3
Summary of the Concordance of HMPAO SPECT and CT Findings Based on Visual Interpretation

	Complete	Partial	None
Minor	9	2	9
Major	14	13	6

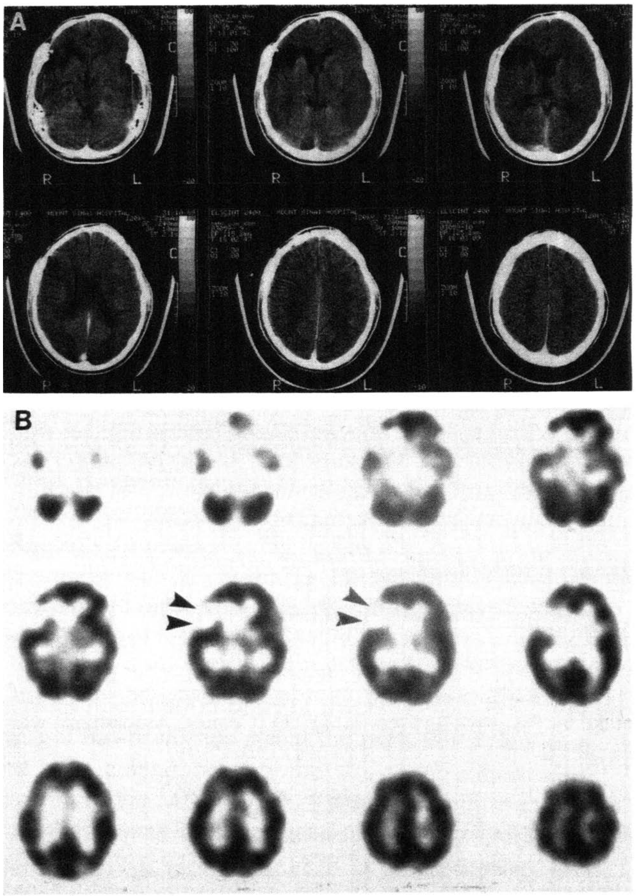

FIGURE 2. A 20-yr-old male who suffered a major head injury during a motor vehicle accident. The patient struck his right fronto-temporal region and sustained multiple, non-depressed skull fractures, which resulted in an extended LOC. Current symptomatology: marked decline in academic performance. (A) Selected images from CT, performed 40 mo after trauma, illustrate large region of encephalomalacia in right inferior frontal and anterior temporal lobes. (B) HMPAO SPECT images (transaxial) performed 36 mo after trauma, show a region of absent perfusion (arrow-heads) corresponding to that seen on CT.

Thus, as might be expected, for the more severely injured patient, there is an increased probability of an abnormality being detected by both imaging modalities.

Figure 2 shows an example of complete concordance in a young male following a motor vehicle accident. In this case, both the CT and HMPAO SPECT scans demonstrated abnormalities in both location and extent. Figures 3 and 4 illustrate findings giving rise to a pattern referred to as partial concordance. In Figure 3, the abnormalities seen with CT underestimated the region of abnormal perfusion found with the HMPAO SPECT scan. Figure 4, however, is an example of the converse where the CT abnormalities are more extensive than the rCBF abnormalities. Finally, an example of a case where no concordance occurred is shown in Figure 5. In this case, the CT scan was interpreted as normal, but abnormalities were discovered on the HMPAO SPECT study. It is interesting to note that in this case an MRI was also performed and interpreted as being normal.

Further analysis of the results are given in Table 4. Table 4A shows that of all TBI patients who had a minor head injury and a normal HMPAO SPECT 8/8 (100%) showed complete concordance with the CT. That is, CT was also found to be normal. In contrast, of the TBI patients sustaining a major TBI and having a normal HMPAO SPECT, 3/3 (100%) had normal CT scans. The abnormality in all three cases consisted of some cerebral atrophy. Table 4B examines those TBI patients who had a normal CT scan. Of those who had a minor TBI, 8/15 (53%) showed complete concordance by having a normal HMPAO SPECT. The findings, however, are quite different for TBI patients with a major head injury. In the latter case, 7/7 (100%) of the patients showed abnormalities on the HMPAO SPECT despite having a normal CT.

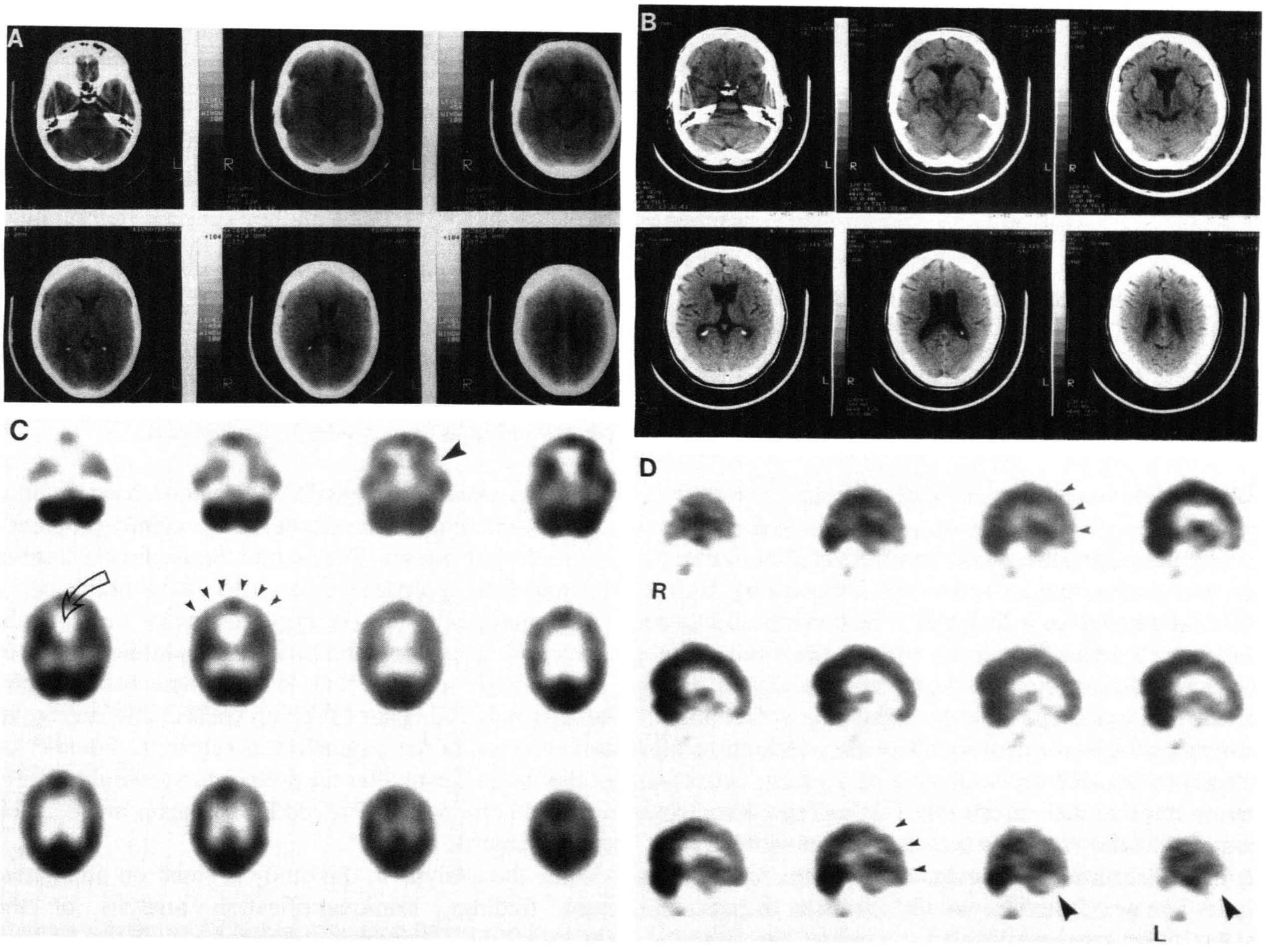

FIGURE 3. A 37-yr-old female who suffered a major head injury during a motor vehicle accident. The patient struck her right periorbital region with resultant intermittent coma (PTA = 7 wk). Current symptomatology: decreased memory, indecision, and noise intolerance with hyperacusis. (A) Selected images from CT at time of trauma show an intracranial contusion in the right inferior frontal lobe. (B) Selected images from a repeat CT, 27 mo after trauma, reveal atrophic changes in the frontal and temporal lobes bilaterally. HMPAO SPECT images, (C) transaxial and (D) sagittal, obtained at same time as second CT (27 mo). Diffusely decreased perfusion of the cortex of the frontal and temporal lobes bilaterally (small arrowheads). In addition, there is decreased perfusion in subcortical region anteriorly (curved open arrow). A focal region of decreased cortical perfusion is present in the left inferior frontal lobe (large arrowheads).

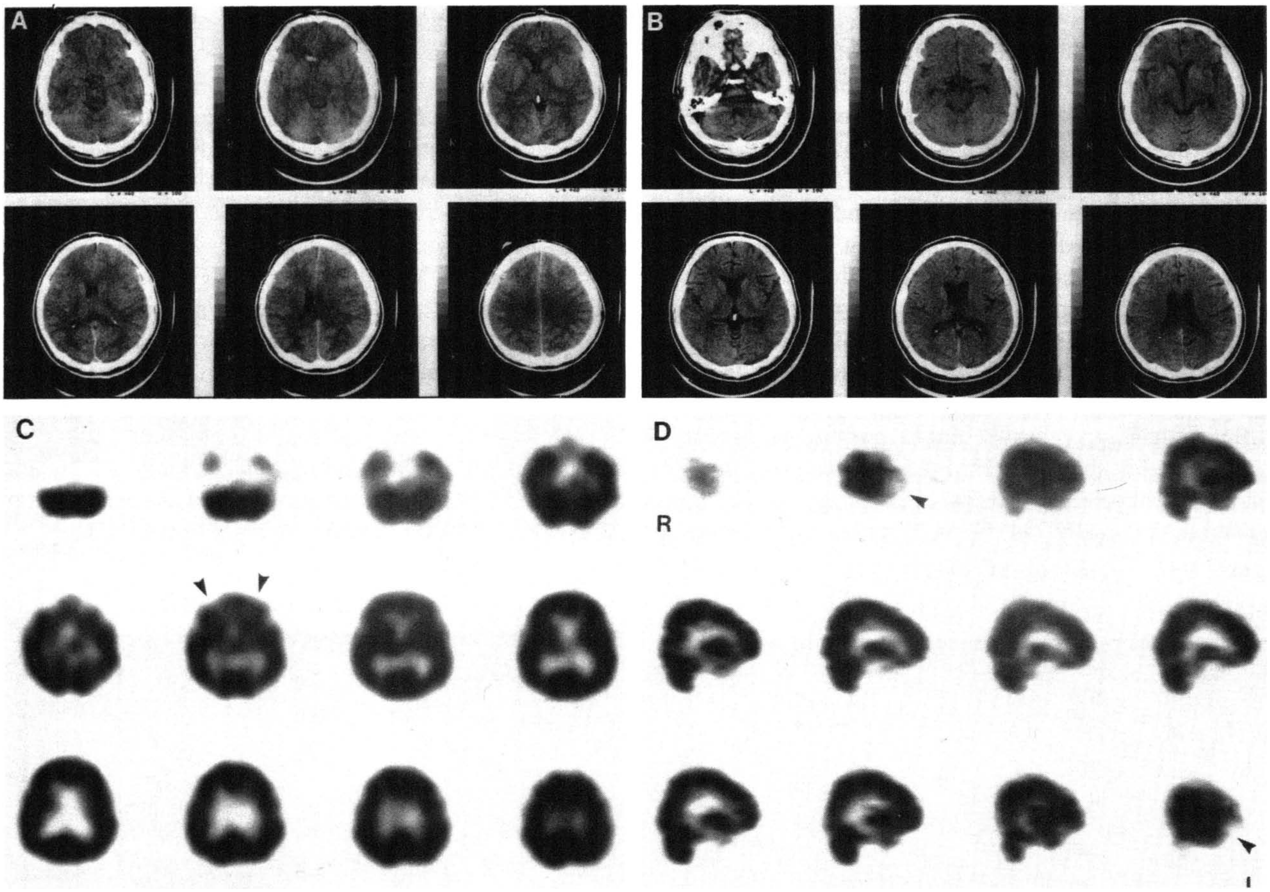

FIGURE 4. A 35-yr-old male who suffered a major head injury in a car accident. (GCS = 6 and PTA = 4 wk). Current symptomatology: headaches, cognitive deficits, and inability to cope. (A) Selected images from CT at time of trauma showed a small left subdural hemorrhage and intracerebral contusions located in the left frontal lobe and anterior forceps of corpus callosum. A mild mass effect is present. (B) Subsequent CT scan, 24 mo later, shows cerebral atrophy in the frontal and temporal lobes bilaterally (with left-sided predominance), as well as left parietal and occipital regions. HMPAO SPECT images, (C) transaxial and (D) sagittal, obtained 56 mo after trauma, show only minimal perfusion deficits in the inferior frontal lobes bilaterally (arrowheads).

DISCUSSION

Strict criteria for patient selection were chosen to maximize the chance that any detected abnormality most probably resulted from a TBI itself. The hope in selecting patients with a single TBI was to correlate the mechanism of injury (i.e., force vectors) to the pattern of abnormalities detected. This was not possible. Most patients were injured in a motor vehicle accident in which the mechanism of injury never involved a pure force (i.e., uniform anterio-posterior translational direction). The unknown contribution of secondary sequelae (i.e., mass effect with herniation) (*37,38*) further compounded the problem of such an analysis. The next criterion was the exclusion of patients with any other previous insult (i.e., infarct or abscess). This criterion is reasonably self-evident. However, infarction is also related to the age restriction of 50 yr or less. This age restriction was instituted to preclude problems of nonsymptomatic infarcts. Previous work (*10*) in functional imaging has already described some of the perfusion deficits seen with various psychiatric diseases. Similarly, drug abuse can affect rCBF due to either an associated psychiatric condition contributing to the abuse: infarct, (e.g., secondary to cocaine abuse) or atrophy (e.g., secondary to alcohol abuse). The remaining exclusion criteria were therefore implemented to address these problems.

The choice of 6 mo or more postinjury was thought sufficient to allow for stabilization of anatomical detail at a macroscopic level (*12,14*). It is possible that synaptic plasticity may still occur (*39*) with consequent increase in functional use of the parenchymal substrate. Whether or not this is significant after the 6-mo interval would require correlation of serial HMPAO SPECT imaging and detailed neuropsychiatric testing.

While the analysis in this study is based on qualitative visual findings, semiquantification analysis of the HMPAO SPECT scans was attempted in both the TBI and NC patient groups. However, in view of the fact that any part of the brain, including the cerebellum (*22,27*), may be affected in a TBI patient, it was difficult to choose a common reference region which would be unaffected in all patients. Normalization of regional activity to global or hemispheric activity may be another method of relative quantification but when a major region of the brain is

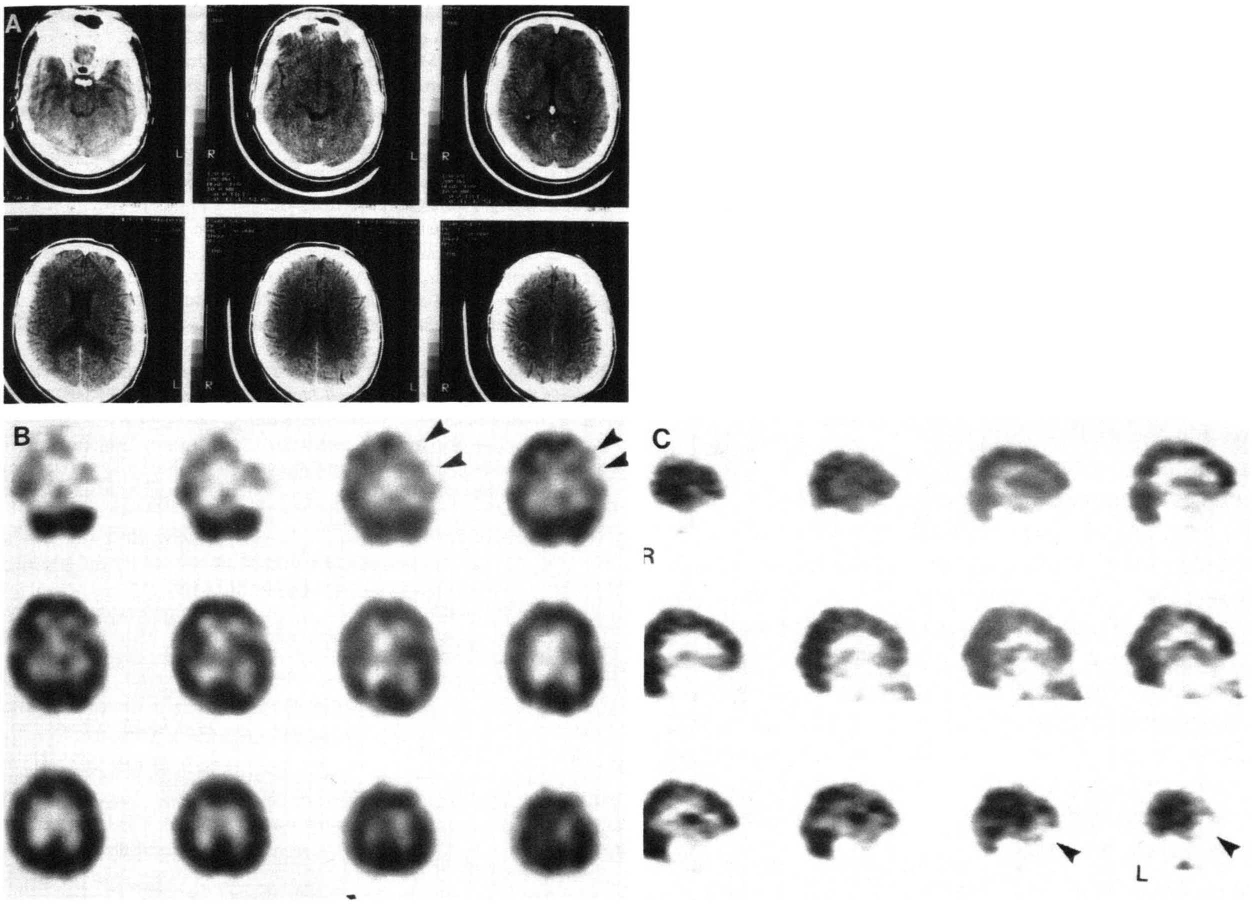

FIGURE 5. A 50-yr-old male who suffered a minor head injury during MVA (LOC = 5 min, GCS = 14 and PTA = 6 hr). Current symptomatology: decreased memory and concentration, emotional lability. (A) Selected images from CT, performed 53 mo after trauma. No abnormalities were detected. (Note: MRI scan performed at same time was also reported as normal). HMPAO SPECT images, (B) transaxial and (C) sagittal, also obtained 53 mo after trauma. Focal deficits are noted in the left inferior frontal and left anterior temporal lobes (arrowheads).

abnormal such relative quantification is likely to underestimate the abnormal regions. Thus, in the present study, data analysis was based solely on visual interpretation.

TABLE 4

A. Patients with Normal HMPAO SPECT Studies Who Have Been Subgrouped Based on Trauma Severity and CT Findings

Minor TBI	8
Normal CT	8
Abnormal CT	0
Major TBI	3
Normal	0
Abnormal	3

B. Patients with Normal CT Studies Who Have Been Subgrouped Based on Trauma Severity and HMPAO SPECT Findings

Minor TBI	15
Normal HMPAO	8
Abnormal HMPAO	7
Major TBI	7
Normal HMPAO	0
Abnormal HMPAO	7

Although regional subcortical perfusion abnormalities were detected on visual inspection, no systematic attempt was made to detect diffuse white-matter changes. This was difficult to assess because white matter perfusion is normally much less than cortical grey matter perfusion. In view of a known diffuse axonal type of injury in TBI patients (*5*), a more rigid method of data analysis which includes white matter and also takes ventricular size or regional brain volume into account, would be appropriate for future studies. This requires an effective method of quantifying the SPECT data.

This study has shown that HMPAO SPECT is more sensitive than CT in the detection of abnormalities of the brain in TBI victims. For the minor TBI group, abnormalities were more frequently detected with HMPAO SPECT than with CT. As the severity of the injury increased, the detection rate of CT, relative to that of HMPAO SPECT, also increased. However, so did the percentage of cases with partial concordance. The majority of these partial concordance cases showed abnormalities on the HMPAO SPECT that were either more severe and/or frequent than those seen with CT. It should be noted that there were some cases where CT abnormalities were present despite a normal HMPAO SPECT scan. In these latter cases, the CT abnormality detected was that of cerebral atrophy. Compared to CT, MRI would probably increase the detection rate of abnormalities in brain parenchyma. However, like CT, it is a morphological modality. Thus, with the use of both functional and morphological modalities that complement each other, a better understanding of TBI patients with neurological, neuropsychiatric and/or neuropsychological complaints may ensue.

While HMPAO SPECT can assess the functional integrity of the brain via its imaging of rCBF, the role of this modality in TBI patients may be more far reaching. It may evolve that the method for classifying TBI based on the criteria of the variables surroundings the accident or clinical indices of injury severity during the immediate post-injury time period (i.e., GCS) are not accurate in the assessment of long-term prognosis of the patient. Rather, inspection for serial improvement in rCBF (e.g., via HMPAO SPECT) and thereby recovery of the perfusion deficit to the brain may be a better prognosticator than the previously used criteria. Once the recovery of any perfusion deficit has plateaued for a set time period, further significant recovery may not be forthcoming. A longitudinal study including both functional and anatomical imaging in tandem with detailed neuropsychiatric and neurological testing is warranted.

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