Prospective Evaluation of Technetium-99m-HMPAO SPECT in Mild and Moderate Traumatic Brain Injury

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We prospectively evaluated the contribution of 99mTc-HMPAO SPECT in patients who have sustained acute, mild or moderate head trauma. Methods: Forty-two patients formed the first subgroup of moderate trauma (ModTr) and 25 patients formed the second subgroup of mild trauma (MiTr). All 67 patients underwent an initial SPECT (Tinit) within 4 wk after a closed cranial trauma. After a mean interval of 3 mo from the time of Tinit, all patients were clinically re-evaluated; those with an abnormal Tinit underwent a repeat SPECT (Trpt) as well. All SPECT studies were visually graded by agreement of three observers adjudging a score ranging from 0 (no lesions) to 4. Results: For the group as a whole (ModTr + MiTr), the following results could be derived: (1) in 32/33 Tinit negative cases, clinical symptoms had resolved; (2) the positive predictive value of Tinit was only 20/34 (59%); (3) the sensitivity for the repeat SPECT was 19/20 (95%). Conclusion: Our results show that: (1) SPECT alterations correlate well with the severity of the trauma; (2) a negative initial SPECT study is a reliable predictor of a favorable clinical outcome; (3) in cases with a positive initial SPECT, a follow-up consisting of a combination of SPECT and clinical data is necessary; (4) in patients suffering from postconcussive symptoms, SPECT offers an instrument to objectivate sequelae.

Key Words: technetium-99m-HMPAO; traumatic brain injury; SPECT


Alterations in regional cerebral blood flow (rCBF) have been described after craniocerebral trauma (I–6). In a study of patients who were all in a state of diminished consciousness after having sustained a head trauma, Abdel-Dayem et al. (3) clearly proved that 99mTc-HMPAO SPECT is more sensitive than CT, enabling an earlier detection of a larger number of lesions. The authors also found that SPECT lesions were larger than the corresponding CT abnormalities, and that SPECT perfusion patterns could be helpful in predicting the prognosis of post-traumatic injuries.

Roper et al. (7) compared 99mTc-HMPAO SPECT and CT in 15 patients with an acute closed-head injury. This study suggested that SPECT is most useful in the detection of focal (rather than diffuse) blood flow alterations that are not seen on CT. It also suggested that two hemodynamically different traumatic contusions could be identified, those with a decreased CBF (detectable with SPECT) and those with a blood flow equal to that of the surrounding brain tissue.

Gray et al. (8) compared 99mTc-HMPAO SPECT to CT in a population of patients with a remote history of traumatic brain injury. Particularly in the subgroup of minor trauma, SPECT was more sensitive than CT, enabling the demonstration of regional brain dysfunction in the presence of morphological integrity.

The present study was set up to evaluate the incidence, the extent and the evolution of CBF changes after mild or moderate head injury and to determine whether SPECT can play a role in the objectivation of traumatic sequelae in patients presenting with postconcussive symptoms. We studied the relationship between SPECT results and the severity of craniocerebral trauma, and we evaluated the correlation between the evolution of CBF disturbances measured by serial SPECT and the clinical course.

MATERIALS AND METHODS

Patient Population and Study Design

The study population consisted of 67 patients, 41 male and 26 female, with a mean age of 35 yr (age range: 11–71 yr), all having sustained a closed-cranial trauma. In 95% of these cases, the trauma was caused by a car, motorcycle or bicycle accident. Subjects were excluded from the study if they had presented a previous cranial trauma, epilepsy or other neurological disorders, psychiatric disease, drug or alcohol abuse, a CT showing important cortical atrophy or focal lesions (such as arachnoid cysts) unrelated to the trauma, or an unreliable anamnesis concerning the trauma.

All 67 patients underwent an initial 99mTc-HMPAO brain SPECT study (Tinit) and a CT within 4 wk after the trauma (26 patients within 3 days; 24 patients between 4 and 7 days; 10 during the second wk; 7 patients between 2 and 4 wk after the trauma).
All SPECT studies were performed, at most, 4 days after the CT scan.

Patients were divided into two subgroups (9). Forty-two patients who had presented a coma (Glasgow Coma Scale ≥11), a retrograde amnesia (<24 hr) and/or an abnormal CT (related to the trauma) were classified in a first subgroup of moderate trauma (ModTr). The remaining 25 patients, who were referred for minor neurological complaints, but had no history of loss of consciousness or retrograde amnesia and had no CT abnormalities, formed a second subgroup of mild trauma (MilTr).

After a mean time interval of 3 mo (range 2.7–3.2 mo) from the time of Tinit, all patients were clinically re-evaluated. Only those with an abnormal Tinit systematically underwent a repeat SPECT (Trpt). During this period, no medication that would alter cerebral perfusion was given.

**Clinical Evaluation**

All patients underwent the same testing, which consisted of a classical complete neurological examination and questioning concerning postconcussive symptoms based on the list of symptomatology given by Rutherford et al. (10). Each subject also had to perform a memory test and a concentration test. If no signs and no symptoms were recorded, a patient was considered "clinically negative."

**SPECT Imaging**

SPECT imaging was performed after intravenous injection of 740 MBq of 99mTc-HMPAO (Ceretec, Amersham, UK). The radiopharmaceutical was prepared according to the manufacturer's prescription with fresh eluate and injected within 20 min after its preparation. Patients were injected in a quiet and dimly lit room. Imaging started 15–30 min after injection.

Tomographic images were obtained using a single-head rotating gamma camera (Toshiba GCA-901A) equipped with a low-energy, high-resolution collimator and connected to a dedicated Toshiba computer (GMS-550U). Data were collected from 60 projections in the 140 keV photopeak (20% window) over 360° in 64 × 64 matrices, with an acquisition time of 30 sec/view. A zoom factor of 1.5 was used. The acquisition data were corrected for nonuniformity according to Toshiba specifications. Orthogonal transverse, coronal and sagittal planes were generated by filtered back-projection using a Butterworth filter (cutoff 0.4 cm−1; order 7), followed by orbitomeatal reorientation of the reconstructed volume. For visual inspection, attenuation correction was not performed (11). The final data set used for interpretation consisted of 2-pixel thick (5.6 mm/pixel) transaxial, coronal and sagittal slices. Each set of images was normalized to its maximal pixel count and a lower threshold of 15% was set on a 256 “spectrum” color scale.

**Data Analysis**

All 99mTc-HMPAO SPECT studies were first visually graded independently by three experienced observers without knowledge of the clinical data, adjudging a score of zero (no lesions) to four. Each lesion was scored from one to three, according to the volume and the severity of the hypoperfusion (12–14): one = small (5.6–11.2 cm3) lesion with moderately decreased perfusion (tracer uptake reduced with 10%–20% compared to contralateral side or to 55%–70% of maximum); two = large (>11.2 cm3) lesion with markedly decreased perfusion or small lesion with markedly decreased perfusion (tracer uptake reduced with >20% compared to contralateral side or to <55% of maximum); three = large lesion with markedly decreased perfusion. In patients with multiple lesions the scores were added up to a maximum of four.

**RESULTS**

**Subgroup of Moderate Trauma (ModTr)**

The results collected from the ModTr subgroup are summarized in Figure 1.

**Initial Evaluation.** Tinit was positive in 25/42 (60%) patients (mean SPECT score 1.9). CT abnormalities were found in 10/42 of ModTr patients. In 3/10 of these patients, Tinit was negative whereas CT showed a very small cortical infarction in one patient, a white matter infarction in another and a small hemorrhagic contusion in a third. In all three cases, the CT lesion size was <0.5 mm. CT lesions found in the seven other patients concerned very thin epidural hematomas, hemorrhagic contusions and a cerebellar infarction. Tinit was normal in 17/42 (40%) patients.

**Follow-up.** Repeat SPECT studies (Trpt), only performed in Tinit positive cases, were still abnormal in 18/25 patients. However, the lesions showed an improvement in 10/18 patients. In 5/18 cases no change was found and in 3/18 subjects the score increased. In all three patients, the SPECT score changed from one to two, caused by a more pronounced relative hypoperfusion, from −15% to −25%. In all three patients, clinical abnormalities were still present at the time of re-evaluation. The global evolution is reflected by a significant decrease of the SPECT score. A mean Trpt score of 1.6 was calculated, which is significantly smaller (p < 0.05) than the corresponding Tinit score. In 13/18 of these Trpt-positive patients, clinical signs...
and/or complaints were still present, whereas 5/18 patients were symptom-free. No correlation was found between the persistence of symptoms and the persistence of perfusion abnormalities in a particular region of the cerebral cortex.

Trpt was normal in 7/25 patients, with 6/7 patients having no more symptoms. In 16/17 patients with a normal Tinit, who were only clinically re-evaluated, symptoms had completely resolved. One patient still presented with mild post-concussive symptoms, consisting of headache and memory disturbances.

Figure 2 shows an example of complete normalization of the SPECT scan in concordance with the total disappearance of symptoms.

Subgroup of Mild Trauma (MiITr)

The results obtained in the MiITr subgroup are summarized in Figure 3.

Initial Evaluation. Tinit was abnormal in 9/25 (36%) patients, (mean SPECT score of 1.3) which is significantly smaller (p < 0.05) than the Tinit score in the Tinit positive cases of the ModTr subgroup. Tinit was normal in 16/25 (64%) patients.

Follow-up. Trpt still showed lesions in 2/9 patients, but without a significant score change compared to the corresponding Tinit results. In 6/7 patients, clinical abnormalities were still presented. Trpt was negative in 2/9 patients. Both had no more symptoms.

In 16/16 patients with a negative Tinit, the clinical evaluation was normal.

Group as a Whole (ModTr + MiITr)

In 34/67 (51%) patients, initial SPECT studies (Tinit) showed perfusion deficits, whereas 33/67 (49%) patients were normal.

For the totality of Tinit, 55 lesions were identified. These were predominantly localized in the left temporal, temporoparietal and frontotemporal areas (22/55 lesions), both frontal (13/55 lesions) and both occipitoparietal (11/55 lesions) regions. The remaining lesions were found in other cortical areas. The results obtained for the group in its totality are summarized in Tables 1 and 2.

The predictive value of an initially negative $^{99m}$Tc-HMPAO SPECT study (Tinit $-$) for a favorable clinical evolution (Clin $-$) can be calculated as the probability, P (Clin $-$ / Tinit $-$), which is 32/33 (97%), Clin representing the clinical status of the patient at the time of re-evaluation.
The positive predictive value of $T_{\text{init}}$, $P(\text{Clin}+|\text{Clin}+)$, is $20/34 = 59\%$.

In 9/34 (26%) patients with an abnormal $T_{\text{init}}$, $T_{\text{rpt}}$ is negative and corresponds to an absence of clinical signs or symptoms in 8/9 (89%) of these patients.

In 25/34 (74%) patients with an abnormal $T_{\text{init}}$, $T_{\text{rpt}}$ still showed lesions though with a significantly ($p < 0.05$) improved score. In 19/25 (76%) of these patients the lesions corresponded to the persistence of clinical abnormalities; 6/25 (24%) patients were asymptomatic.

The sensitivity of the initial SPECT study ($T_{\text{init}}$) in patients with clinical sequelae ($\text{Clin}+|\text{Clin}+\cap T_{\text{init}}$) was calculated as $P(T_{\text{init}}+|\text{Clin}+) = 20/21 = 95\%$; for the repeat study ($T_{\text{rpt}}$), the sensitivity $P(T_{\text{rpt}}+|\text{Clin}+) = 19/20 = 95\%$ and the total fraction of patients presenting symptoms and an abnormal SPECT $P(T_{\text{init}},T_{\text{rpt}}+|\text{Clin}+) = 19/21 = 90\%$.

The specificity of $T_{\text{init}}$,$rpt$ or $P(T_{\text{init}},rpt-|\text{Clin}-) = 32/46 = 65\%$.

The fraction of asymptomatic patients ($\text{Clin}-\cap T_{\text{init}}$) with an abnormal $T_{\text{init}}$ who still have SPECT lesions $P(T_{\text{init}}+|\text{Clin}-) = 6/14 = 43\%$.

**DISCUSSION**

Several studies have already pointed out the superior sensitivity of brain perfusion SPECT compared to CT in the detection of traumatic brain injury (3,6–8). However, the exact place of SPECT in a scheme of clinical work-up and follow-up of craniocerebral trauma still must be better defined, particularly in cases of mild to moderate trauma.

The present study was set up to evaluate the role of cerebral blood flow SPECT in the clinical management of patients having sustained a mild or moderate closed-head trauma. In particular, we were interested in estimating the usefulness of $^{99m}\text{Tc}-\text{HMPAO}$ SPECT as a prognosticator of the clinical evolution after the trauma, by evaluating the evolution of cerebral blood flow disturbances in relation to the clinical course.

In most studies, the duration and grade of the coma and the duration of the retrograde amnesia are used in defining the severity of the trauma (3,7,8). The patient population in our study was divided into two subgroups ("mild" or "moderate" trauma), according to the clinical appearance of the patient at the moment of and shortly after the trauma, (9) and the presence or absence of CT lesions related to the trauma. More precisely, the grouping was based on the presence or absence of coma (Glasgow Coma Scale ≥11) and/or retrograde amnesia (<24 hr) and/or a CT lesion. This classification was preferred because, in many cases, the exact duration of the coma and the retrograde amnesia is very difficult, if not impossible, to assess. This is often due to particular circumstances of the trauma and/or the subjectiveness of hetero- or auto-anamnestic data preventing an accurate clinical judgement.

An important feature of our patient population is that the whole study group is composed of rather mild traumata. The large majority of our patients can be considered as having sustained a concussion. In order to emphasize the mild character of many traumas, but also to permit a correlation between CBF changes and the severity of the trauma, we classified patients who had no loss of consciousness, no retrograde amnesia and no CT lesions, in a separate subgroup of mild trauma.

Scanning patients in the early post-traumatic period seems to be most appropriate (15) in increasing the diagnostic yield. Moreover, it provides a basal study closely related to the trauma, which can afterwards be used as a reference for comparison to the follow-up study. All our patients were examined as quickly as possible after the trauma (39% within 3 days, 75% within the first week after the trauma). Clinical and, in cases with an abnormal initial scan, SPECT re-evaluation were performed after a mean time interval of 3 mo. No precise data are available that would enable an exact assessment of the appropriate time of a follow-up examination. In a study of 145 patients with concussions from minor head injuries, Rutherford et al. (11) found 49% to have no more symptoms about 6 wk after the accident. Therefore, from a clinical point of view and for reasons of compliance, a period of about 3 mo seems to be acceptable, allowing patients to clinically recover from the consequences of the trauma. In mild traumas, it is reasonable to expect patients to become free of symptoms within this time interval. In our own study population, clinical sequelae appeared to be absent in 70% of patients after approximately 3 mo.

Our data confirm that brain perfusion SPECT is more sensitive than CT in the detection of post-traumatic cere-
bral abnormalities and that a negative CT in the early postevent period does not exclude functional lesions.

In the subgroup of moderate trauma, 60% of the initial SPECT studies showed perfusion disturbances. In the mild trauma subgroup, 36% of these scans were positive, but with a significantly lower score of perfusion abnormality, suggesting that SPECT lesions closely correspond to the severity of the trauma.

The perfusion deficits found in this study were most frequently located in the left temporal, temporoparietal and frontotemporal areas (40%), both frontal (24%) and both occipitoparietal regions (20%). Most of our patients were injured in a car, motorcycle or bicycle accident not allowing, in most cases, determination of the precise direction or mechanism of the causative traumatic force. Moreover, in cases with reliable information concerning the mechanics of the trauma, the regions of hypoperfusion did not often correlate with the site of impact or the contralateral site ("contrecoup effect"). An analog observation had already been made in a previous study by Ducours et al. (15). Consequently, no clear explanation can be given for the predominance of left-sided lesions in the temporal and adjacent regions. Other studies (15,16) have demonstrated a similar distribution pattern of perfusion abnormalities, mostly located in the temporal and frontal lobes and the parieto-occipito-temporal junction. Experimental studies on the mechanics of cerebral trauma have highlighted that these areas are particularly susceptible to traumatic injury (17,18).

Our study shows a very high negative predictive value of the initial cerebral blood flow SPECT in both subgroups (97% for the totality of the patient population). In that way, brain perfusion SPECT offers clinicians a powerful tool in predicting a favorable outcome after a mild to moderate closed-head trauma. On the other hand, the predictive value of a positive initial SPECT is only 59%, emphasizing the need for further follow-up studies.

In 26% of the patients with an initially positive SPECT study, the repeat scan was negative; this course was combined to a symptom-free status in 89% of these cases. Such an evolution suggests that the initial blood flow alterations might be ascribed to (sub)acute post-traumatic functional abnormalities. Within a couple of months these can spontaneously disappear with the clinical disturbances (no cerebrovascular treatment had been given).

In 74% of cases with a positive initial scan, the repeat SPECT remained abnormal, though in many cases a clear improvement was observed. In 76% of these patients, the persistence of SPECT lesions was accompanied by residual postconcussive symptoms. The remaining 24% were completely free of symptoms. Regarding this last subgroup of persistent subclinical cerebral blood flow changes, some important observations must be made. All but one of these cases were found in the subgroup of moderate trauma, and all had a normal CT. Possibly, the evolution of these functional lesions is somewhat slower and/or, during the time interval of 3 mo, the symptomatology could have improved quicker. On the other hand, it is well known that psychosocial factors can influence the symptoms expressed by patients having sustained a trauma (19,20).

Our results demonstrate that repeat SPECT shows perfusion deficits in 95% of patients with persistence of postconcussive symptoms and/or clinical signs. This high SPECT "sensitivity" represents an important instrument in the objectivation of otherwise undetectable sequelae. Indeed, many patients keep presenting clear postconcussive symptoms, but an objective proof confirming the presence of an organic dysfunction is often lacking because classical techniques, such as CT and EEG, are frequently normal in these subjects.

CONCLUSION

Our results suggest that cerebral perfusion SPECT offers the clinician a useful tool in the evaluation and follow-up of patients after acute, mild or moderate traumatic brain injury. SPECT alterations correlate well with the severity of the trauma. A normal initial SPECT is a reliable predictor of a favorable clinical outcome. On the other hand, an abnormal initial SPECT is not sufficient as a prognosticator of the outcome. In the follow-up, the combination of SPECT and clinical data should be considered. SPECT offers an objectivation of sequelae in patients suffering from postconcussive symptoms.

REFERENCES

Predicting Outcome in Traumatic Brain Injury: What Role for rCBF/SPECT?

Traumatic brain injury (TBI) represents a major public health problem. According to the National Head Injury Foundation, Inc., there are over two million TBIs annually in the US. Of the survivors, approximately 70,000 to 90,000 will sustain permanent loss of cognitive and/or motor function. The annual costs for dealing with this patient population approaches $25 billion (from Facts About Traumatic Brain Injury, distributed by the National Head Injury Foundation, Inc., Washington, DC, undated).

Not all patients suffer severe trauma, many fall into the category of moderate to minor trauma. These patients typically do not require hospitalization, but may have some loss of consciousness and retrograde amnesia, as in the case of moderate traumatic brain injury. Patients with minor TBI will often present with minimal neurological complaints. There are two major issues to consider when dealing with moderate and minor TBI. One is the ability to identify the extent of the brain damage and its relation to the patient’s clinical presentation. Another is predicting the resolution of the symptoms. Regional cerebral blood flow/SPECT may provide data relevant to both these questions.

There is increasing evidence that rCBF/SPECT is a viable technique for detecting cortical lesions following TBI. Regional cerebral blood flow/SPECT imaging frequently reveals a greater number of lesions than either CT or MRI in patients with moderate or minor TBI (1–5). The lesions visualized with SPECT in this patient population tend to be larger than those seen on CT or MRI. However, unless it can be shown that the regional changes identified by SPECT, not seen on CT or MRI, better account for the patient’s clinical findings, these modality differences are of little value.

Jacobs et al. (6) go beyond the question of CT versus SPECT in the evaluation of the TBI patient. Their paper contributes to the assertion that rCBF/SPECT is useful for predicting clinical outcome in moderate and minor TBI based on the initial SPECT scan. In addition, their data make clear that patients with persistent clinical symptoms will continue to have abnormal follow-up SPECT scans. Such findings, if corroborated in other laboratories, are of significance for the future treatment of these patients. For example, it is possible to hypothesize that further rehabilitation for patients with positive clinical and SPECT findings at the end of three months may yield little in the way of continued improvement.

The observation that a negative initial SPECT scan predicts resolution of symptoms within a three month period is also significant. Jacobs et al. do not indicate whether their patients were involved in head trauma rehabilitation programs. Study designs involving SPECT as a predictor of outcome in TBI should include information regarding treatment and rehabilitative efforts.

A corollary question is whether the greater lesion size and/or number of abnormal regions reported for SPECT is a better indicator of clinical severity than CT or MRI findings. Although Jacobs et al. (6) did not address this issue directly, it is possible to make this assertion based on their data. Of particular significance was their finding in patients with minor trauma who had negative CTs. Patients with persistent positive SPECT scans remained symptomatic, and those with negative scans remained negative on follow-up. The situation is less clear for their moderate TBI group. Most patients who were still symptomatic had positive repeat SPECT scans. It is not known if the CTs for these patients were negative.

Much has been made of the observation that SPECT picks up more and larger lesions than anatomic imaging. However, to say that more lesions are detected by SPECT or that these lesions are larger than those seen on CT/MRI is not by itself a sufficient argument in favor of SPECT as the imaging modality of choice in moderate and minor TBI. The perceived characteristics of the lesions detected...
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