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EDITORIAL

Metabolic Consequences of Acute Brain Trauma: Is There a Role for PET?

Brain injury following head trauma is a serious central nervous system disorder that affects several hundred thousand individuals in the United States every year. Appropriate assessments of the degree of damage caused is essential in initiating the required therapies and determining prognosis.

Over the past two decades, we have witnessed many significant developments in the diagnosis and management of patients with head injury. The introduction of a single and reproducible grading system, the Glascow Coma Scale (GCS), was a major step toward categorizing patients with regard to the severity of injury sustained (*1*). The utilization of x-ray computed tomography in the early 1970s and MRI in the 1980s also made immeasurable contribution to the detection and characterization of a variety of lesions caused by head trauma (*2,3*). Despite such important advances, however, much needs to be accomplished to understand the underlying pathophysiologic and metabolic alteration that accompany two major injuries to the brain: ischemic cell damage and diffuse axonal injury (DAI). Ischemic cell damage occurs in over 90% of patients who succumb to head injury (*4*). In many victims of head injury with postmortem ischemic or hypoxic lesions, no predisposing disorders are found prior to death. Diffuse axional injury is probably the basic pathological damage in head injury (*5*). This injury occurs as a result of stretching and tearing of axons in the white matter of the cerebral hemisphere and the brainstem.

In addition, it has been demonstrated that brain injury results in a series of molecular events that lead to accumulation of toxic products which eventually result in ischemia—reperfusion type of injury (*6–8*). This is considered the underlying mechanism for ischemia noted with various insults to the brain, including trauma or subarachnoid hemorrhage and stroke (*9*). Although postmortem studies have revealed clear evidence for focal and global ischemia in patients with head trauma, no convincing clinical evidence for such a complication following head injury has been demonstrated by researchers (*10–15*). Most ischemic changes have been observed in the "frontoparietal" watershed areas. These changes were noted in patients who were severely injured (*16*). Most head trauma investigators believe that ischemia plays a distinct role in the clinical outcome of patient with head trauma.

A powerful methodology which has allowed investigation of hemodynamic and metabolic changes in the brain is the noninvasive measurement of absolute cerebral blood flow (CBF) and some metabolic parameters following the intravenous administration or inhalation of ^{133}Xe (*17*). Utilizing this powerful technique, the relationship among CBF, cerebral metabolic rate for oxygen (O_2) utilization ($CMRO_2$) and the level of consciousness have been elucidated (*14, 15*). With this technique, a measurement of only limited brain tissue sample is made utilizing detectors which are placed over the skull. Metabolic rates for oxygen ($CMRO_2$) can be calculated by measuring arterio-jugular O_2 difference and multiplying by the average CBF estimates from the detectors selected for this purpose (*15*). Obviously, this technique provides information about superficial structures of predetermined sites in the brain. In spite of these shortcomings, much knowledge has been gained by studying patients with acute head injury. It has been noted that $CMRO_2$ is consistently depressed in head-injured comatose patients and whose magnitude is correlated well with GCS (*15*). However, an interesting observation has been made when CBF and $CMRO_2$ were compared in such patients. In about half of the patients, CBF and $CMRO_2$ are coupled, as seen in normal states. In the remainder, an uncoupling of blood flow and metabolism is clearly demonstrated. In these patients, relative hyperemia is detected despite significantly reduced $CMRO_2$. In other words, CBF exceeds the metabolic requirements of the tissue perfused. In patients with hyperemia, there is a high incidence of increased intracranial hypertension. In spite of its major contributions to the understanding of hemodynamic and metabolic consequences of head injury, the ^{133}Xe CBF technique cannot demonstrate evidence for cerebral ischemia in this disorder.

The use of regional functional imaging techniques such as SPECT, PET (*18*), nuclear magnetic resonance (NMR) (*19,20*) spectroscopy and stable xenon x-ray CT (*21,22*) has provided a unique opportunity to visualize and quantify several important physiologic and metabolic parameters that are considered important in head injury.

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By now, it is well established that PET or SPECT cannot distinguish between functional abnormalities as a consequence of structural damage and those without such findings (*18,23–25*). Thus, it is necessary to compare PET images to the corresponding anatomical images generated by MRI or CT. In general, cerebral dysfunction can extend far beyond the confines of anatomical lesions (*26–28*) and may even appear in locations distant from the site of trauma. It has been shown that approximately 33% of anatomical lesions are associated with larger and more widespread metabolic abnormalities and as much as 42% of PET abnormalities are not associated with any anatomical lesions (*29*).

Functional abnormalities secondary to lesions such as cortical contusions and intracranial hematomas are confined primarily to the site of injury. However, subdural and epidural hematomas often cause widespread dysfunction and may even affect the contralateral hemisphere (*28*). Diffuse axonal injury has been found to cause widespread cortical hypometabolism and there is a marked decrease in metabolism in the parieto-occipital (particularly the visual cortex) cortex (*29*).

Crossed, as well as ipsilateral cerebellar diaschisis seen as hypometabolism, has been found in head injury patients with supratentorial lesions (*30*). A good correlation between the severity of head trauma as measured by the GCS and the extent of whole brain hypometabolism as measured by FDG-PET has been demonstrated (*29*). In addition, other studies have shown that hypometabolism on PET correlates with neuropsychological testing (*31,32*). Global and regional metabolic rates have been found to improve as patients recover from head trauma (*27,28*).

In this issue of *JNM,* Yamaki et al. (*33*) describe cerebral hemodynamic and metabolic changes in three patients with severe diffuse brain injury as determined by PET. These investigators were able to measure the regional (CBF) oxygen extraction fraction (OEF), cerebral blood volume (CBV), $CMRO_2$, cerebral metabolic rate for glucose (CMRglc) and the cerebral metabolic ratio ($CMRO_2$/CMRglc). The patients suffered a severe head injury with a GCS of 4–5 on admission. Although CBF was noted to be reduced in all three patients, the corresponding $CMRO_2$ was disproportionately lower in one patient. In this patient, OEF and CMRglc were significantly elevated while the metabolic ratio was relatively low. In the remaining two patients, all measured parameters were significantly reduced and indicated matching blood flow and metabolism. Although the first patient died as a result of his injury, the other two made good recoveries. These investigators indicate that evidence of long-lasting anaerobic glycolysis and high OEF and low metabolic ratios is a poor prognostic indicator.

Yamaki et al. speculate that the trigger for anaerobic glycolysis and increased OEF was not related to protracted tissue hypoxia as reported in the literature. This finding corroborates those from experimental studies of cerebral concussion where elevated lactate levels were demonstrated which were attributed to derangement of brain energy metabolism in the absence of substance limitations (*34,35*). Similar findings have also been reported in rat experiments utilizing ^{14}C-deoxyglucose autoradiography (*36*). This observation represents a new concept that should be confirmed with further studies and in a larger subject population. Performance of a comprehensive PET examination, which includes measurement of various physiological and metabolic parameters, is not feasible in most patients who have severe head injury and are heavily dependent on life-support systems.

The use of NMR spectroscopy may further improve our understanding of metabolic derangements occurring in these patients (*19,20*). Unfortunately, such studies are time-consuming and cannot be sucessfully performed in critically ill patients who depend on external life-support systems.

Modern imaging techniques provide powerful means for detecting and monitoring complex and serious physiological, metabolic and structural alterations following head injury. Research with these new techniques should aim at the following goals:

- To detect ischemic lesions that develop soon after trauma to the head. Previous methodologies have failed to reveal evidence for this in pathologic states. PET, and possibly NMR spectroscopy, with high resolution and sensitivity may provide good prospects for accomplishing this goal.
- Accurately diagnose diffuse axonal injury to define the extent of damage and forecast prognosis. Modern high-resolution MRI techniques may visualize minor but clinically relevant lesions, but functional imaging, including activation studies, may play a critical role in defining the consequences of such lesions.
- Delineate reversible from irreversible lesions. Therapeutic interventions should be carefully assessed to demonstrate that such measures do not result in further damage or convert a reversible lesion to irreversible injuries.

CONCLUSION

By utilizing modern imaging and non-imaging techniques, limitations in imaging brain function following injury could be accurately assessed. Every effort should be made to demonstrate that the remaining normal brain is trained to compensate for the lost function (cerebral plasticity). Functional imaging techniques, particularly activation studies, with PET, SPECT or MRI, will be of considerable importance in accomplishing these goals. Modern rehabilitation will increasingly use imaging methodologies to determine the efficacy of various therapeutic interventions in such patients.

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Demonstration of Frontal Hypoperfusion in Benign Exertional Headache by Technetium-99m-HMPAO SPECT

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We present a case of benign exertional headache (BEH) in a 15-yr-old boy. The patient suffered from exclusively exercise-induced headaches with migraine-like accompanying symptoms. No pathology could be detected by routine cardiovascular or neurological examinations by CT. The postexercise ^{99m}Tc-HMPAO brain SPECT performed during the provoked headache attack showed asymmetric bifrontal hypoperfusion. A second ^{99m}Tc-HMPAO study during a symptom-free phase under resting conditions was normal. The detection of impaired regional cerebral blood flow (rCBF) by ^{99m}Tc-HMPAO brain SPECT indicates a perfusion-related pathology in this type of headache. Analysis of rCBF with ^{99m}Tc-HMPAO in larger studies could be helpful in the clarification of BEH pathogenesis.

Key Words: benign exertional headache; technetium-99m-HMPAO; SPECT

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Benign exertional headache (BEH) was first described in 1932 by Tinel et al. (*1*). This type of headache occurs, by definition, during different physical activities increasing the intrathoracic pressure such as coughing, breath-keeping, laughing, crying, running, etc. It is generally of short duration and can be well localized (*2,3*). The same form of headache has also been reported in relation with the tumors of the posterior fossa and the lesions of foramen magnum (*3*). The coexistence of symptoms such as nausea, vomiting and photophobia during the attacks lets one suppose a close relation between BEH and migraine (*4*). The clinical relevance of regional cerebral blood flow (rCBF) analysis by radioactive tracers is now widely accepted. Regional hypoperfusion in different types of migraine has been demonstrated by ^{133}Xe imaging and more recently by ^{99m}Tc-HMPAO SPECT studies (*5–8*). The well-known superiority of SPECT over planar imaging in regional analysis and the ready availability of ^{99m}Tc-HMPAO, make the latter the most popular method. We present a case of reversible cerebral hypoperfusion demonstrated during a provoked BEH attack using ^{99m}Tc-HMPAO brain SPECT.

CASE REPORT

A 15-yr-old boy suffering from exclusively exercise-induced headache (after running approximately 30 m) was admitted to the neurology department of our university hospital. The headache began always suddenly during exercise in both frontal regions, was pulsating and lasted between 12 and 48 hr. It was often accompanied by photophobia, nausea and vomiting. Analgesics such as acetyl salicilic acid or paracetamol were effective to only some extent. There was no family history of migraine. Neurological examination during a symptom-free phase was normal. Routine biochemistry, telecardiography, electrocardiography, brain CT as well as electroencephalography were unremarkable. BEH was

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