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Acute Cerebral Perfusion CT Abnormalities Associated with Posttraumatic Amnesia in Mild Head Injury

Zwany Metting,1 Lars A. Rödiger,2 Bauke M. de Jong,1 Roy E. Stewart,3 Berry P. Kremer,1 and Joukje van der Naalt1

Abstract

Posttraumatic amnesia (PTA) is a common symptom following traumatic brain injury. Although this transient memory deficit implies specific impairment of higher brain function, the actual pathophysiology of PTA is not well understood. The aim of this study was to assess regional cerebral hemodynamics with perfusion computed tomography (CT) in patients during PTA following mild head injury compared to patients with resolved PTA. A total of 74 patients with mild head injury without structural abnormalities on a non-contrast CT scan were included and compared to 25 healthy controls. Two patient groups were defined: (1) a PTA group that was scanned during the episode of PTA (n = 34), and (2) a post-PTA group scanned after resolution of PTA (n = 40). The PTA group had significantly reduced cerebral blood flow (CBF) in the frontal grey matter (41.78 [SD 7.4] versus 44.44 [SD 6.2] mL/100 g/1 min, p = 0.023), and caudate nucleus (44.59 [SD 6.2] versus 47.85 [SD 7.7] mL/100 g/1 min, p = 0.021), compared to the post-PTA group. Thus in patients with mild head injury, PTA is associated with cerebral perfusion abnormalities in specific cortical and subcortical regions.

Key words: mild head injury; perfusion computed tomography; posttraumatic amnesia

Introduction

Traumatic head injury is frequently followed by a transient state of anterograde amnesia accompanied by confusion and disorientation, referred to as posttraumatic amnesia (PTA). (Ahmed et al., 2000) The hallmark of this syndrome is reflected by an inability to store current events (Russell and Smith, 1961), often in combination with restlessness and agitation after injury. It has been established that the duration of PTA in head-injured patients is of prognostic significance (Bishara et al., 1992; Cifu et al., 1997; Ellenberg et al., 1996), particularly in mild-to-moderate head injury (Naalt van der et al., 1999). However, the pathophysiological basis of PTA is not well understood, and only a few studies have examined patients during the amnestic state. Most functional imaging studies performed so far were not able to provide further insight into the neuronal mechanisms that underlie PTA, because most of the patients were examined after the resolution of PTA, or information about whether patients were examined during or after PTA was lacking. Furthermore, most hemodynamic imaging studies of PTA were performed with single-photon emission CT (SPECT), a semi-quantitative technique with low spatial resolution and restricted tracer availability (Gowda et al., 2006; Lorberboym et al., 2002). With the increasing application of perfusion CT imaging in trauma patients (Soustiel et al., 2007; Wintermark et al., 2004), it has become feasible to quantitatively assess cerebral perfusion parameters, particularly in the acute phase after injury.

The objective of this study was to examine regional cerebral hemodynamics with perfusion CT imaging in patients with mild head injury, providing an index for local neuronal function, either during PTA or after the resolution of PTA. The results were compared with the cerebral hemodynamics of healthy controls.

Methods

Patients

Patients with acute traumatic brain injury were identified as candidates for enrolment in this prospective study during a 2-year period, between May 2005 and June 2007. Inclusion criteria were (1) age 18–65 years, (2) mild head injury as defined as an initial Glasgow Coma Scale (GCS) score between 13 and 15, (3) the presence of posttraumatic amnesia (PTA), and (4) no intracranial abnormalities seen on non-contrast CT scan. An earlier study published in 2009 comprised the same study population (Metting et al., 2009). The duration of PTA was defined as the time between injury and the return of
orientation and continuous memory encoding. PTA was established prospectively by means of a questionnaire (Naal van der et al., 1999). If the PTA had resolved before the patient arrived at our emergency department, its duration was estimated retrospectively. Two distinct groups were distinguished: (1) a PTA group with patients who were scanned during their episode of PTA, and (2) a post-PTA group with patients who were scanned after resolution of PTA. Patients with a history of neurological disease, psychiatric disorders, mental retardation, addiction to alcohol or other drugs, and those ineligible for long-term follow-up were excluded. Pregnancy, and a history of diabetes, nephropathy, and iodine allergy were additional exclusion criteria. Written informed consent was obtained from the patients, or from either family or next of kin if the patient was unable to provide consent himself or herself. The control group consisted of 25 healthy volunteers (10 males and 15 females), with a mean age of 37 years (SD 12.2 years). Healthy controls fulfilled identical exclusion criteria as the patient group, and also provided written informed consent. Both parts of the study, those addressing patients and healthy controls, were separately approved by the medical ethical committee of the University Medical Center Groningen.

**Imaging**

Patients underwent imaging after admission at the emergency department immediately after consent was obtained. CT images were obtained by a Siemens Somatom Sensation 64-row CT scanner (Siemens Medical Systems, Erlangen, Germany). First a standard non-contrast CT was performed followed by a perfusion CT scan. Two adjacent 14.4-mm thick

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**FIG. 1.** Lower slab with regions of interest (ROIs). In this slab six ROIs were placed in the white matter, and six ROIs were placed in the cortical grey matter. Also, two ROIs were placed in the caudate nuclei, and two ROIs were placed in the thalami (A, frontal white matter; B, temporoparietal white matter; C, occipital white matter; D, frontal grey matter; E, temporoparietal grey matter; F, occipital grey matter; G, caudate nucleus; H, thalamus).
slabs were positioned at the level of the thalamus, basal ganglia, and third ventricle, and at the level of the centrum semiovale and the lateral ventricles, and 40 mL of a non-ionic iodinated contrast agent (Visipaque 270 mg/mL) was power injected at a rate of 5 mL/sec, followed by a 20 mL saline infusion. After a 5-sec prep delay, a continuous scan was initiated with the following parameters: 80 kV, 100 mAS, and 1 rotation/sec, for a total duration of 46 sec. Post-processing was performed by an experienced neuroradiologist (L.R.) using TeraRecon perfusion software (TeraRecon Inc., San Mateo, CA). A gamma variate fitting curve was applied. The deconvolution algorithm produced two sets of colored parameter maps for cerebral blood flow (CBF), mean transit time (MTT) and cerebral blood volume (CBV). Using a saved set of regions of interest (ROIs), quantitative values for CBF were generated in the frontal, temporal, occipital white and grey matter, caudate nucleus, and thalamus. The lower slab is displayed in Figure 1. The neuroradiologist (L.A.R.) who examined the CT images was blinded to study group. No sedatives were given during the procedure.

Statistical analysis

All statistical analyses were done using SPSS version 16.0 (SPSS Inc., Chicago, IL). Perfusion data from the two slabs were averaged.

Analysis of variance (ANOVA) was used to compare CBF, MTT, and CBV values of patients who were still in PTA during scanning (the PTA group), with those obtained from patients with resolved PTA (the post-PTA group). Patient data were also compared with those of a healthy control group. These analyses were stratified by the eight anatomical regions in the frontal, temporal, and occipital white and grey matter, caudate nucleus, and thalamus. The presented p values were adjusted for age and gender by using them as covariates in the statistical analyses. Statistical significance was set at p < 0.05.

Results

Patient characteristics

Seventy-six patients fulfilled the initial inclusion criteria. A total of 74 patients were finally analyzed, as in 2 patients it remained unsure if they were scanned during or after their period of PTA. Patient characteristics are displayed in Table 1. In the PTA group 34 patients were included, and in the post-PTA group there were 40 patients. In all patients, perfusion CT scanning was completed without complications, and no adverse reactions to the contrast material occurred. The mean time between injury and perfusion CT scanning was 3.9 h (SD 2.2 h). Most injuries (63.5%) were caused by traffic accidents, predominantly bicycle-related injuries (36.5%). None of the patients suffered from circulatory instability or needed mechanical ventilation. Alcohol consumption prior to the accident was present in 28 patients, and no intoxication was found. In 3 patients pulmonary injury was diagnosed, and one patient had an abdominal injury. In 10 patients fractures were present, distributed over the extremities (4), ribs (3), and spinal column (3), while 3 patients had a skull and/or skull-base fracture, and 9 patients suffered from facial fractures.

PTA and regional perfusion abnormalities

Regional CBF, MTT, and CBV values were obtained for both patient groups during or after the episode of PTA. The regional CBF values are displayed in Figure 2. Patients who were scanned during their period of PTA showed significantly reduced CBF in both the frontal grey matter (41.78 [SD 7.4] versus 44.44 [SD 6.2] mL • 100 g⁻¹ • min⁻¹; p = 0.023), and the caudate nucleus (44.59 [SD 6.2] versus 47.85 [SD 7.7] mL • 100 g⁻¹ • min⁻¹, p = 0.021), compared to the post-PTA group. Furthermore, there was a significant correlation (R = 0.626, p < 0.001) between the CBF in the frontal grey matter and the caudate nucleus. The MTT in the thalamus was significantly increased in patients scanned during PTA (4.22 [SD 1.2] versus 3.78 [SD 0.7] sec; p = 0.039). No significant relation between CBF and PTA was present.

When compared to healthy controls, a significant decrease in CBF in the frontal grey matter was observed in patients scanned during PTA (41.78 [SD 7.4] versus 46.71 [SD 5.5] mL • 100 g⁻¹ • min⁻¹, respectively; p = 0.009). Significant, although less strong, decreases in CBF of the PTA group compared to healthy controls were also found in the caudate nucleus and occipital grey matter. The MTT was significantly decreased in patients scanned during PTA compared to healthy controls (3.87 [SD 0.7] versus 4.42 [SD 0.7] sec, respectively; p = 0.009), whereas no significant differences in CBV could be discerned. In post-PTA patients, no significant differences in CBF in the various regions were found compared with healthy controls.

A longer duration of PTA was associated with a significant decrease of CBF in the frontal grey matter (R = −0.330; p = 0.006), which was more pronounced in the right hemisphere. This relation is visualized in Figure 3. A cut-off point could not be discerned. No relation was present between the length of time between injury and scanning and CBF values. Alcohol consumption was neither related to changes

<table>
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<th>Table 1. Patient Characteristics</th>
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<td><strong>PTA group (n = 34)</strong></td>
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<td>Time between injury-perfusion CT hours (SD)</td>
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<td>Number of patients with alcohol consumption (%)</td>
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GCS, Glasgow Coma Scale; SD standard deviation, CT, computed tomography; PTA, posttraumatic amnesia.
in cerebral perfusion, nor did it influence the relationship between cerebral perfusion and PTA.

Discussion

In this study cerebral hemodynamics was studied with perfusion CT imaging in patients who were scanned either during or after PTA following mild head injury. During the amnestic state, significant cerebral perfusion decreases were observed in the frontal grey matter and caudate nucleus, indicating locally-impaired neuronal function in this patient category.

To our knowledge, no previous studies have addressed the hemodynamics of patients during and after their period of PTA, although with SPECT studies regional perfusion abnormalities have been observed in patients with a posttraumatic amnestic period and a normal non-contrast CT scan. The extent of these SPECT abnormalities was found to be related to the duration of PTA, with hypoperfusion predominantly seen in the frontal and temporal lobes (Gowda et al., 2006; Lorberboym et al., 2002). With xenon CT, abnormalities were also seen in the frontotemporal region in a small group of mild head-injured patients with an amnestic period, compared to healthy controls (Nariai et al., 2001).

The pathophysiological mechanism of PTA is not well understood, and various mechanisms have been suggested, such as focal edema, direct injury, and ischemia, and even perfusion changes due to remote alterations of neuronal activity have been suggested (Ahmed et al., 2000). The involvement of the temporal lobes, and the hippocampus in particular, in memory processes have been well described, as bilateral damage to these structures may cause severe anterograde amnesia (Scoville et al., 1957; Zola-Morgan et al., 1986). However, it remains questionable whether the pathological mechanism is of PTA, which by definition are transient, may be extrapolated from conditions with permanent anterograde amnesia associated with structural abnormalities. The resolution of PTA suggests the presence of functional changes as opposed to structural changes. It is important to keep in mind that the patients examined in our study were analyzed either during or after an amnestic state, and that in all of our patients the PTA ultimately resolved.

A condition comparable to PTA is transient global amnesia (TGA), because of its temporarily stunned memory. TGA is characterized by transient anterograde amnesia. Involvement
of various interconnected cerebral regions like the hippocampal formation, thalamus, cingulate gyrus, striatum, and cortices has been demonstrated (Baron et al., 1994; Schmidtke et al., 1998; Warren et al., 2000; Yamane et al., 2008). CBF changes in various regions during TGA have a tendency to resolve spontaneously, whereas PET studies do not show signs of ischemia (Fanti et al., 2000). Schmidtke and colleagues demonstrated transient cortical hypoperfusion in TGA patients, with concomitant subcortical hypoperfusion only present in those patients whose amnesia was fully expressed during SPECT imaging (Schmidtke et al., 1998). Recent neuroimaging data have shown that the level of detection of lesions with diffusion-weighted MR imaging in TGA is a threshold phenomenon, dependent on the timing of imaging (Bartsch and Deuschl, 2010).

In our current perfusion CT study, we were also able to detect cortical hypoperfusion in the frontal lobes, with involvement of the subcortical regions in patients during an amnestic state. The most important finding of the current study is the significantly lower CBF seen in the frontal grey matter. When analyzing left-right differences, a longer duration of PTA was predominantly associated with decreased CBF in the right hemisphere. This latter finding thus appears to be consistent with functional MRI studies of working memory that described a functional relationship with right frontal activity (McAllister et al., 2006). When a patient exhibits PTA, functional MRI shows a dysfunction in working memory, and hence decreased activity would be expected during the acute phase. Memory is not localized to a single center in the brain, but is subserved by a distributed network, including the frontal cortices (Eustache et al., 1997; Fazio et al., 1992; Fletcher and Henson, 2001; Jonides et al., 1993; Schlosser et al., 2006; Shallice et al., 1994). The prefrontal cortices in particular appear to play an important role in explicit memory retrieval (Blumenfeld and Ranganath, 2007; Eustache et al., 1997; Funahashi, 2006). Local decreases in perfusion, which are indicators of local neuronal activity, may in this respect reflect functional deprivation due to lesions in remote areas of such a network (Raichle, 1998). This might also explain the correlation between significantly decreased CBF in the frontal grey matter and the caudate nucleus in our patient group.

One of the most intriguing aspects of PTA is the resolution of the amnestic state. Reabsorption of edema may account for recovery of function in some cases, but to explain the tremendous variation seen in the duration of PTA, other reversible mechanisms must be operative. The concept of diaschisis, introduced as a cerebral variant of spinal shock, refers to the disruption of intact neuronal systems by localized lesions in distant but associated neurons or their connections, and this may play an important role in PTA (Ahmed et al., 2000; Feeney and Baron, 1986; Riese, 1958). The origin of this functional disruption is not well understood, although a role for acetylcholine has been suggested (Ahmed et al., 2000; Dixon et al., 1995; Goldberg et al., 1982; Nissen et al., 1987). We postulate that the involvement of the frontal cortices in memory retrieval and the principle of diaschisis provide an explanation for the significantly decreased CBF seen in the frontal grey matter and the caudate nucleus in our PTA group.

It should be noted that the differences in CBF between the PTA group and the post-PTA group were relatively small compared to the ischemic values described in studies of patients with severe head injury (Bouma et al., 1991), or cerebral ischemic stroke (Eastwood et al., 2002). The differences, however, were significant, and might reflect impaired functioning caused by more subtle local damage, or reduced network functioning caused by more subtle damage in remote areas (Raichle, 1998). Furthermore, in an earlier study we found decreased cerebral perfusion in mild head-injured patients to be of prognostic value, while in none of the patients were ischemic levels reached (Metting et al., 2009).

Although it has been possible to study the amnestic state with perfusion CT, some limitations of our study have to be mentioned. The reversibility of the amnestic state was not studied by serial measurements in the same patient. The main reason for not performing repeated perfusion CT scans was the additional radiation exposure in a category of patients that are in general directly discharged from the hospital. Another issue is whether the time point of scanning post-injury was a confounding factor with regard to the CBF differences we found. However, no significant relationship between the time of scanning and CBF was found. In addition, patients with an increased duration of PTA showed a larger decrease in CBF, which is an argument against the assumption that lower CBF occurs in the early hours after injury, with subsequent improvement over time, as seen in severe head injury (Bouma et al., 1991).

One could argue that the injuries in our patient group were not severe enough to induce decreases in CBF that reached ischemic levels, and thus only reflected temporary dysfunction instead of structural damage. The non-contrast CT scan on admission showed no abnormalities, whereas CT scans in severe head injury demonstrate abnormalities (Bouma et al., 1991). For future studies, it would be interesting to compare the perfusion CT results with MRI studies using susceptibility-weighted imaging (SWI), and diffusion tensor imaging (DTI)-weighted sequences, to detect ischemic or axonal abnormalities. With regard to the absence of perfusion changes in the temporal cortex, it should be considered that partial volume effects from the skull may influence measurements of the basal temporal lobes. Further, the quantitative determination of distinct sub-profiles of memory impairment in the acute phase was not feasible, because elaborate neuropsychological tests could not be applied due to the relatively short duration of PTA. Hence our results should be clarified by future neuropsychological examinations of residual memory impairment.

Notwithstanding the acknowledged limitations, this study uniquely demonstrated regional changes in cerebral hemodynamics in patients that were suffering from PTA. Significant cortical and subcortical cerebral perfusion abnormalities were revealed in the prefrontal cortex and the interconnected caudate nuclei. Further studies should be done to explore the relationships of these hemodynamic changes in the acute phase after head injury with results of MRI studies and neuropsychological tests to evaluate long-term outcomes.

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Author Disclosure Statement

No competing financial interests exist.

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