Brain and Cognition 86 (2014) 24–31

Contents lists available at ScienceDirect

Brain and Cognition

journal homepage: www.elsevier.com/locate/b&c

Cerebral perfusion and neuropsychological follow up in mild traumatic brain injury: Acute versus chronic disturbances?

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ARTICLE INFO

Article history:
Accepted 21 January 2014
Available online 18 February 2014

Keywords:
Mild traumatic brain injury
Perfusion CT
Neuropsychological testing
Emotion recognition
Executive function

ABSTRACT

In a subgroup of patients with mild traumatic brain injury (TBI) residual symptoms, interfering with outcome and return to work, are found. With neuropsychological assessment cognitive deficits can be demonstrated although the pathological underpinnings of these cognitive deficits are not fully understood. As the admission computed tomography (CT) often is normal, perfusion CT imaging may be a useful indicator of brain dysfunction in the acute phase after injury in these patients.

In the present study, directly after admission perfusion CT imaging was performed in mild TBI patients with follow-up neuropsychological assessment in those with complaints and a normal non-contrast CT. Neuropsychological tests comprised the 15 Words test Immediate Recall, Trailmaking test part B, Zoo Map test and the FEEST, which were dichotomized into normal and abnormal. Perfusion CT results of patients with normal neuropsychological test scores were compared to those with abnormal test scores.

In total eighteen patients were included. Those with an abnormal score on the Zoo Map test had a significant lower CBV in the right frontal and the bilateral parieto-temporal white matter. Patients with an abnormal score on the FEEST had a significant higher MTT in the bilateral frontal white matter and a significant decreased CBF in the left parieto-temporal grey matter. No significant relation between the perfusion CT parameters and the 15 Words test and the Trailmaking test part B was present.

In conclusion, impairments in executive functioning and emotion perception assessed with neuropsychological tests during follow up were related to differences in cerebral perfusion at admission in mild TBI. The pathophysiological concept of these findings is discussed.

1. Introduction

The majority of the patients with mild traumatic brain injury (TBI) recover within weeks to months without specific therapy. However, a subgroup continues to experience disabling symptoms that interfere with their return to work or resumption of social activities (Benedictus, Spikman, & Naalt van der, 2010; Naalt van der, Zomeren van, Sluiter, & Minderhoud, 1999b; Rimel, Giordani, Barth, Boll, & Jane, 1981; Stambrook, 1990; Wood, 2004). These symptoms comprise headaches, dizziness, memory problems and difficulties with learning new tasks (Kraus et al., 2005).

There is no consensus in the literature regarding neuropsychological deficits in mild TBI. Most studies have suggested that cognitive deficits occur shortly after injury with the impairment usually dissipating at 1–3 months post injury (Belanger, Curtiss, Demery, Lebowitz, & Vanderploeg, 2005; Dikmen, McLean, & Temkin, 1986; Frencham, Fox, & Maybery, 2005; Levin et al., 1987b; Ponsford et al., 2000; Rohling et al., 2011; Schretlen & Shapiro, 2003). Still other, often smaller, studies have shown that persistent impairment can be present in patients with mild TBI (Barth et al., 1983; Bernstein, 2002; Kwok, Lee, Leung, & Poon, 2008; Leininger, Gramling, Farrell, Kreutzer, & Peck, 1990; Ruff et al., 1994; Vanderploeg, Curtiss, & Belanger, 2005). Impairments in a range of cognitive domains at long-term follow up have been documented after mild TBI, (Konrad et al., 2010) with most deficits involving attention and concentration (Binder, Rohling, & Larrabee, 1997; Kwok et al., 2008; Ruff et al., 1994), memory, (Barth et al., 1983; Bernstein, 2002; Dikmen et al., 1986;

Abbreviations: FR, frontal; PAR-TE, parieto-temporal; WM, white matter; GM, grey matter; R, right hemisphere; L, left hemisphere.

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http://dx.doi.org/10.1016/j.bandc.2014.01.012
0278-2626/

Frencham et al., 2005; Leininger et al., 1990) speed of information processing (Frencham et al., 2005), verbal fluency (Kwok et al., 2008), and executive functions (Frencham et al., 2005; Levin et al., 1987b). In particular executive functions are considered higher order regulatory functions that rely on the integrity of frontal but also temporal and parietal areas (Duncan, 2013; Stuss, 2011; Vincent, Kahn, Snyder, Raichle, & Buckner, 2008). In patients with moderate to severe TBI lesions in fronto-temporal areas are frequently found with CT or MRI and associated with deficits in higher order functions (Levine et al., 2013; Spikman, Timmerman, Milders, Veenstra, & Naalt van der, 2012) found that deficits in higher order cognitive functions in patients with TBI were also related to volume loss in parietal and temporal regions. However, in mild to moderate TBI conventional computed tomography (CT) characteristics are not a sufficient predictor of outcome knowing that approximately 20–25% of the patients with mild to moderate TBI with a normal non-contrast CT experience problems with resuming work (Naalt van der, Hew, Zomeren van, Sluiter, & Minderhoud, 1999a). More recent neuroimaging techniques may improve knowledge in the pathology of mild TBI, increase the sensitivity for detecting abnormalities and, hence, allow the development of better prognostic indicators.

Hemodynamic imaging in head injury has gained insight in the pathological mechanisms of TBI although, up till now, only a small number of hemodynamic imaging studies have been performed in the acute phase of mild TBI, in particular single photon emission CT (SPECT) (Audenaert et al., 2003; Gowda et al., 2006; Lorberboym, Lampl, Gerzon, & Sadeh, 2002), Xenon CT (Nariai, Suzuki, Ohta, Ohno, & Hirakawa, 2001) and perfusion CT (Metting et al., 2009). These studies did reveal cerebral perfusion abnormalities in patients with a normal conventional CT scan. In addition, Audenaert and colleagues (Audenaert et al., 2003) assessed a good topographical accordance between SPECT abnormalities and neuropsychological testing in the acute phase, although they did not examine long-term neuropsychological outcome. Nevertheless, to date the precise relation of cerebral perfusion in the acute phase of injury with cognitive functioning during follow up is unclear. Perfusion CT is an imaging modality using the dynamics of the distribution of intravenous contrast to determine cerebral perfusion in the brain, and can easily be performed in the emergency setting. In a previous study on mild TBI we found that perfusion CT abnormalities were predictive for the outcome according to the extended Glasgow Outcome Score (GOSE) (Metting et al., 2009). For this reason we conducted the present study in which we aimed to determine whether brain dysfunction as indicated by perfusion CT imaging at admission is related to abnormal neuropsychological tests during follow up in mild TBI patients with a normal conventional CT. More specifically, we would expect a relation between frontal, parietal and temporal cerebral hypoperfusion and neuropsychological deficits as these brain areas are strongly involved in higher cognitive functions regarding memory, attention, executive and social cognition.

2. Methods

2.1. Participants

Between 2005 and 2007 consecutive patients admitted with acute TBI were prospectively identified for enrolment in this study. Inclusion criteria were (1) age 18–65 years, (2) mild TBI defined as an initial GCS between 13 and 15 and (3) posttraumatic amnesia (PTA). Exclusion criteria were: age, a history of neurological (also previous TBI) or psychiatric disease, mental retardation, addiction to alcohol or drugs, inability to long-term follow up, pregnancy, a history of diabetes, nephropathy and contrast allergy. In this part of the study we only analyzed those patients with no abnormalities on the non-contrast CT.

In total 191 patients were screened for inclusion. Of those, 96 patients had to be excluded for various reasons. Of the 95 included patients, 76 had no abnormalities on the non-contrast CT and were analyzed further yielding a subgroup ($N = 19$) that also obtained neuropsychological testing during follow up, because of posttraumatic complaints. One patient had to be excluded from further analysis because of insufficient effort, hence, 18 patients were suitable for further analysis.

Of all the included patients a written informed consent could be obtained from patients, family or next of kin if patients were unable or inadequate to provide consent. The study was approved by the Medical Ethical Committee (METC) of the University Medical Center Groningen and was in compliance with the Helsinki Declaration.

2.2. Complaints

A checklist of 19 complaints was filled out which contains symptoms that are frequently reported in the literature as part of the sequelae of TBI. This symptom checklist is comparable to the Head Injury Symptom Checklist (HISC) (McLean, Dikmen, Temkin, Wyler, & Gale, 1984) with addition of symptoms not related to concussion. These items were meant to check an increased tendency to complain. To control for the base rates of complaints, subjects were also asked if they experienced any of the complaints before the injury, and if they did, whether these had stayed the same or had worsened since the injury. Hence, a correction could be made in the total number of symptoms if they were already present pre-injury. In addition, they were also asked to qualify their symptoms as occurring seldom (score 1) or often (score 2). In this manner the total number of (posttraumatic) complaints and the severity of symptoms (i.e. sum score of occurrence of complaints) were recorded.

2.3. Perfusion CT imaging

The CT scans were made on a Siemens Somatom Sensation 64-row CT scanner (Siemens Medical Systems, Erlangen, Germany). First a standard non-contrast CT of the brain was performed, followed by a perfusion CT. In our patient group, the non-contrast CT scans were all evaluated by a radiologist on call. A central re-review was performed within a few days after trauma by an experienced neuroradiologist (L.R.). Two adjacent 14.4 mm thick slabs, perpendicular to the hard palate, were positioned at the level of the thalami, basal ganglia and third ventricle and at the level of the centrum semiovale and the lateral ventricles. A 40-ml volume of a non-ionic iodinated contrast agent (Visipaque 270 mg/mL) was power-injected at a rate of 5 ml/s, followed by a 20-ml saline chase. After 5 s delay, a dynamic scan was initiated with the following parameters: 80 kV, 100 mA, and 1 s per rotation for a duration of 46 s. The estimated radiation dose was acceptable to the standards of our Medical Ethical Committee. Post-processing was also performed by an experienced neuroradiologist (L.R.) using TeraRecon perfusion software (TeraRecon Inc., San Mateo, CA, USA). 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). By using a digitally saved preset of regions of interest (ROIs) quantitative values for CBF, MTT and CBV were generated in the frontal, parieto-temporal and occipital white and grey matter on the two slabs. These two slabs were averaged and stratified for the regions and the three perfusion parameters. In this part of the study we only analyzed the frontal and parieto-temporal ROIs.