Behavioural Brain Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Behavioural Brain Research

journal homepage: www.elsevier.com/locate/bbr

Research report

Both hemorrhagic and non-hemorrhagic traumatic MRI lesions are associated with the microstructural damage of the normal appearing white matter

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HIGHLIGHTS

- Non-hemorrhagic lesion presence is related to decreased microstructural integrity.
- Basal ganglia area microbleeds are related to decreased microstructural integrity.
- Focal MRI pathology evaluation may substitute quantitative diffusion tensor imaging.

ARTICLE INFO

Article history:
Received 29 June 2016
Received in revised form 11 October 2016
Accepted 22 February 2017
Available online xxx

Keywords:
MRI
Traumatic brain injury
Susceptibility weighted imaging
Diffusion tensor imaging
Traumatic microbleeds
Diffuse axonal injury

ABSTRACT

Traumatic microbleeds (TMBs) and non-hemorrhagic lesions (NHLs) on MRI are regarded as surrogate markers of diffuse axonal injury. However, the actual relation between lesional and diffuse pathology remained unclear, since lesions were related to clinical parameters, largely influenced by extracranial factors.

The aim of this study is to directly compare TMBs, NHLs and their regional features with the co-existing diffuse injury of the normal appearing white matter (NAWM) as measured by diffusion tensor imaging (DTI).

Thirty-eight adults with a closed traumatic brain injury (12 mild, 4 moderate and 22 severe) who underwent susceptibility weighted imaging (SWI), T1-, T2 weighted and FLAIR MRI and routine CT were included in the study. TMB (on SWI) and NHL (on T1-, T2 weighted and FLAIR images) features and Rotterdam scores were evaluated. DTI metrics such as fractional anisotropy (FA) and mean diffusivity (MD) were measured over different NAWM regions. Clinical parameters including age; Glasgow Coma Scale; Rotterdam score; TMB and NHL features were correlated to regional NAWM diffusivity using multiple regression.

Overall NHL presence and basal ganglia area TMB load were significantly, negatively correlated with the subcortical NAWM FA values (partial $r = -0.37$ and -0.36; $p = 0.006$ and 0.025, respectively).

The presence of any NHL, or TMBs located in the basal ganglia area indicates diffuse NAWM damage even after adjusting for clinical and CT parameters. To estimate DAI, a conventional lesional MRI pathology evaluation might at least in part substitute the use of quantitative DTI, which is yet not widely feasible in a clinical setting.

Abbreviations: AD, axial diffusivity; DAI, diffuse axonal injury; FA, fractional anisotropy; FLAIR, fluid attenuated inversion recovery; GCS, Glasgow Coma Scale; GRE, gradient recalled echo; MD, mean diffusivity; NAWM, normal appearing white matter; NHL, non-hemorrhagic lesion; RD, radial diffusivity; SWI, susceptibility weighted imaging; TBI, traumatic brain injury; TE, echo time; TI, inversion time; TMB, traumatic microbleed; TR, repetition time.

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http://dx.doi.org/10.1016/j.bbr.2017.02.039
0166-4328/

1. Introduction

Traumatic brain injury (TBI) constitutes a public health problem worldwide [1]. Diffuse axonal injury (DAI) is a substantial pathological component of brain injury, and is highly related to outcome [2]. DAI (or traumatic axonal injury) can occur both in severe and mild TBI [2] at a certain extent. However, in consequence of its microscopic range, it is basically "invisible" to standard TBI imaging protocols.

Interest in the application of susceptibility weighted imaging (SWI) [3] in TBI has recently been increasing rapidly, since it has been shown to be a very sensitive imaging method for the detection of the possible DAI-associated hemorrhagic foci, also known as traumatic microbleeds (TMBs) [4]. SWI is a fully velocity-compensated, high-resolution 3D gradient echo sequence that uses magnitude and filtered-phase information, both separately and in combination, and is therefore able to create a strong contrast for the susceptibility effects of microbleeds [3]. Other imaging methods, such as CT, T2- and T2*-weighted MRI or FLAIR are also able to depict punctual DAI-related lesions, though less reliably than SWI [5–8]. SWI allows patients with a DAI to be dichotomized as hemorrhagic or non-hemorrhagic, and this has been proposed to be of clinical relevance [9,10]. Moreover, the number, localization, type and volume of TMBs have been linked to the severity of clinical state as well as the outcome [7,8,11–19].

Another advanced MRI method, diffusion tensor imaging (DTI), has been proposed to sensitively detect white matter damage itself by a very extensive body of literature [20]. DTI does not only detect Brownian diffusion extent, but also diffusion directionality (anisotropy) and direction [21,22]. Data suggest that the different DTI parameters, such as fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD) and radial diffusivity (RD) may reflect the damage of the white matter [20]. Though the detected actual traumatic DTI parameter alterations vary largely across studies, in the relatively late phases of TBI, studies mostly agree that FA is decreased, while MD is increased due to axonal pathology. However, to date DTI assessment of axonal injury has been based almost exclusively on group analyses, with the use of post-processing computation and statistics [20]. The main reasons limiting the interpretation of the DTI data at a subject level are the high inter-subject variations (even within the healthy population), and the relatively low specificity of DTI to axonal injury.

In contrast to DTI, SWI might be easily applied at an individual level. A conventional, qualitative morphological assessment might define TMB load, extent and anatomical distribution per patient. Therefore, SWI appears to be the most feasible advanced MRI method for the indirect evaluation of axonal damage in a clinical environment, because group analysis and statistics are not necessary for its interpretation.

However, thus far no consensus has been reached concerning the optimal clinical use of SWI, T2*GRE or other MRI modalities including the ones depicting non-hemorrhagic lesional pathology (NHL), in TBI. Studies largely agree that TMBs are related to the clinical severity or outcome, but they are heterogeneous in the aspects of the investigated population size, injury severity, image acquisition method, outcome assessment method, as well as the detection and definition of TMB [7,8,11–19]. Though TMBs are accepted as surrogate markers of DAI, it is of note that they are rather due to microvascular injury, than axonal injury, and these two are not necessarily strictly related. The clinical state of the patient, however is probably rather dependent on the diffuse axonal-, and not microvascular injury.

The main problem in understanding the role of SWI in TBI can be summarized as: SWI data were related to clinical parameters that are largely influenced by extracranial factors and not directly to the actual axonal pathology. For example, Glasgow Coma Scale (GCS) may be influenced by alcohol or drug intoxication and accompanying neurological and psychiatric diseases, outcome scores as the Glasgow Outcome Score [23] may be influenced by the presence of extra-cranial injuries, the therapy and rehabilitation process, and the adherence of the patient, etc. As a consequence, it is still unclear if TMBs, or NHLs, and which lesion parameters (number, volume or localization) are indicating the higher rate of axonal damage.

Theoretically, these issues might be resolved when TMB and NHL parameters are correlated with the simultaneously acquired DTI data, since DTI has been widely accepted to sensitively indicate microstructural damage [20], however, because of its technical features and necessary group analyses, up to now it has been not widely used in a clinical setting.

The purpose of this study is to directly compare the diffuse microstructural injury of the normal appearing white matter as measured by DTI with the clinically readable hemorrhagic and non-hemorrhagic traumatic lesion features in TBI patients, to better understand the association between diffuse axonal injury and lesional pathologies.

2. Methods

2.1. Subjects

This retrospective study was conducted on a database consisting of 66 adults with a closed TBI who underwent the MR imaging protocol (see Section 2.2) from the trauma center at the University of Pécs. Exclusion criteria included a previous documented TBI, any known neurological (including migraine) or psychiatric disease, uncontrolled hypertension, a history of anticoagulant therapy or coagulopathy, or a severe mass lesion or brain distortion precluding reliable DTI analysis. These criteria allowed the inclusion of 38 patients, for clinical and demographic details see Table 1.

20 age- and sex-matched healthy volunteers following the same exclusion criteria were recruited as a control group in the study (see Table 1).

Ethical approval was received from the Institutional Review Board (IRB). Written informed consent was obtained from all the participants (or their legally authorized representatives) in the study.

2.2. Imaging protocol

An acute (<24 h) CT scan was performed for all TBI patients according to the institutional TBI CT protocol. CT scan was not performed for the healthy control group.

MRI data were acquired in the chronic phase after the injury (min. 1 month, average 2 years ± 15 months after the injury). MRI was performed on a Magnetom® TIM Trio© 3 Tesla scanner (Siemens, Enlargen, Germany) with a 12 channel standard head coil. The control group underwent the same MRI protocol as the TBI patients:

The sequences consisted of a high-resolution T1-weighted scan (MP-RAGE), T2-weighted scan, FLAIR, DTI and SWI. After the localizer scanning for proper orientation, shimming was carried out to maximize field homogeneity.

T1-weighted high-resolution images were obtained using a three-dimensional (3D) MP-RAGE sequence (TR/TI/TE = 1900/900/3.41 ms; flip angle = 9°; 160 axial slices; slice thickness = 0.94 mm; no inter-slice gap; field of view [FOV] = 210 mm × 240 mm; matrix size = 224 × 256; receiver bandwidth = 180 Hz/pixel).

T2-weighted images were acquired using a turbo spin echo sequence (TR/TE = 6000/93 ms; flip angle = 120°; 30 axial slices; slice thickness = 4 mm; no inter-slice gap;

Please cite this article in press as: A. Toth, et al., Both hemorrhagic and non-hemorrhagic traumatic MRI lesions are associated with the microstructural damage of the normal appearing white matter, Behav Brain Res (2017), http://dx.doi.org/10.1016/j.bbr.2017.02.039