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Research paper

Microbleeds may expand acutely after traumatic brain injury

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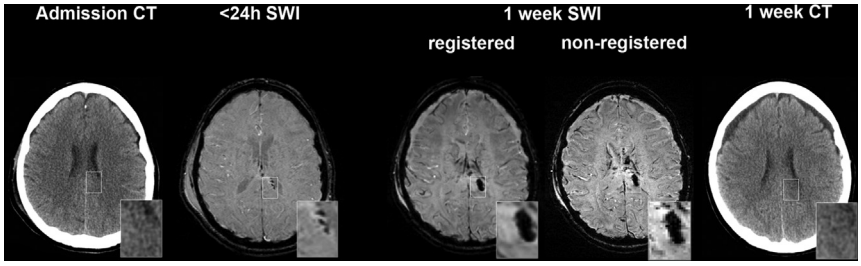
HIGHLIGHTS

- A certain portion of the traumatic microbleeds changed within a week after the injury.
- This change occurred in forms of microbleed expansion and confluence.
- Due to this, both the overall microbleed count and volume was altered.
- Imaging timing may be relevant for optimizing the prognostic utility of this biomarker.

GRAPHICAL ABSTRACT



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ABSTRACT

Background and purpose: Susceptibility weighted imaging (SWI) is a very sensitive tool for the detection of microbleeds in traumatic brain injury (TBI). The number and extent of such traumatic microbleeds (TMBs) have been shown to correlate with the severity of the injury and the clinical outcome. However, the acute dynamics of TMBs have not been revealed so far. Since TBI is known to constitute dynamic pathological processes, we hypothesized that TMBs are not constant in their appearance, but may progress acutely after injury.

Materials and methods: We present here five closed moderate/severe (Glasgow coma scale $\leq$ 13) TBI patients who underwent SWI very early (average = 23.4 h), and once again a week (average = 185.8 h) after the injury. The TMBs were mapped at both time points by a conventional radiological approach and their numbers and volumes were measured with manual tracing tools by two observers. TMB counts and extents were compared between time points.

Results: TMBs were detected in four patients, three of them displaying an apparent TMB change. In these patients, TMB confluence and apparent growth were detected in the corpus callosum, coronal radiation or subcortical white matter, while unchanged TMBs were also present. These changes caused a decrease in the TMB count associated with an increase in the overall TMB volume over time.

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Conclusion: We have found a compelling evidence that diffuse axonal injury-related microbleed development is not limited strictly to the moment of injury: the TMBs might expand in the acute phase of TBI. The timing of SWI acquisition may be relevant for optimizing the prognostic utility of this imaging biomarker.

1. Introduction

Traumatic brain injury (TBI) constitutes a public health problem worldwide [5]. Diffuse axonal injury (DAI) is a substantial pathological component of brain injury, and is highly related to the patient outcome [16]. 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) [21] 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 hemorrhagic components of DAI, traumatic microbleeds (TMBs) [28]. 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 [21]. 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 so than SWI [3,7,10,30]. SWI allows patients with a DAI to be dichotomized as hemorrhagic or nonhemorrhagic, and this has been proposed to be of clinical relevance [9,31]. Moreover, the number, localization, type and volume of TMBs have been linked to the severity of injury and the clinical outcome [1,2,8,10,14,18,30,33].

Other advanced MRI methods, and primarily diffusion tensor imaging, are also sensitive in the detection of axonal injury, but to date these results have been based on group analyses, generally with the use of post-processing computation and statistics [13].

In contrast, SWI might be easily applied at an individual level too. A conventional morphological assessment might define TMB number, extent and anatomical distribution per patient.

However, no consensus has yet been reached as concerns the optimal clinical use of SWI (or T2*GRE) in TBI. Whereas studies largely agree that TMBs are related to the injury severity or outcome, they differ from the aspects of the investigated population size, the injury severity, the image acquisition method, the outcome assessment method, the TMB detection and even the definition of TMB, features that may explain their heterogeneous results.

Another important factor might be the interval between injury and imaging. This has varied widely across and within the published studies (from days to years [10,30]). If microbleeds are not static, but change (in number, extent, etc.) over time, the timing of imaging should be a crucial aspect as concerns the drawing of correct relations with the clinical features. We are aware of only two studies that have longitudinally investigated microbleeds in TBI; they concentrated on the long-term (several months to years) microbleed changes and revealed a slight attenuation in the microbleed visibility, probably due to hemosiderin absorption [20]. However, since acute TBI constitutes dynamic pathological processes, a microbleed status change in the acute phase is also highly possible.

We hypothesized that the microbleed parameters might change in the acute phase of TBI and we present here a follow-up SWI investigation of five TBI patients within the acute period.

2. Subjects and methods

Adults with a severe or moderate closed TBI (Glasgow Coma Scale, GCS < 14), but lacking major intracranial bleeding on the acute CT scans, were recruited prospectively from the trauma center at the University of Pécs in 2015. Exclusion criteria included an age above 50 years, a previously documented TBI, any known neurological or psychiatric disease, uncontrolled hypertension, diabetes, a history of smoking, a history of anticoagulant therapy, any contraindication of acute MRI, or a refusal to provide informed consent (by patient or legally authorized representative). These criteria allowed the inclusion of five patients (for the clinical details, see Table 1). The severe TBI patients received low-molecular-weight-heparin as prophylactic antithrombotic therapy within 24 h after the injury, in accord with the general neuroanesthetic protocols [26]. The clinical outcome was assessed by a neuropsychologist (V.T.) at 6 months after the injury with the use of the Extended Glasgow Outcome Score (GOS-E) [32].

MRI was performed within 24 h after the injury and once again a week later with the same equipment and protocol, which included T1-, T2- and SWI (for technical details, see Table 2).

The TMBs were identified on the SWI scans at both time points by two independent raters (A.T. and a board-certified neuroradiologist T.R.), blinded to the clinical data. The TMBs were defined as punctuate, ovoid or curvilinear hypointensities located in the white matter or white-gray matter border that were clearly not consistent with blood vessels or artefacts. To aid such exclusion of mimicking hypointensities and a more precise anatomical localization, both the high-resolution T1-weighted and the T2 images were registered to the SWI images by using the FMRIB's Linear Image Registration Tool (FLIRT, FSL, FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, Oxford, UK)[15], which allowed a multi-modal assessment of the TMB sites. The TMBs associated with a T1 or T2 signal alteration were not excluded. The TMBs adjacent to contusions or bone-air interface artefacts (e.g. near the mastoid process) were excluded. Only the TMBs identified by both raters were included in the overall number of TMBs per scan.

The the overall TMB volume was then measured with manual tracing tools (FSL [29], FMRIB's Software Library, www.fmrib.ox.ac.uk/fsl, Oxford, UK) by both raters; the averages of the measured data were regarded as the final overall microbleed volume per scan. In order to check on the rating reliability, the raters assessed the overall microbleed volumes twice and the intra- and inter-rater intraclass correlation coefficients were calculated, using the two-way model, absolute agreement mode (MedCalc statistical software version 15.4, Ostend, Belgium) [27].

To allow TMB comparison in the same image orientation and slice position, the SWI scans from different timepoints were co-registered by using FLIRT. On the basis of the image coordinates, the TMBs were tracked on the registered follow-up images, and any possible obvious change (shrinkage, growth, confluence, fragmentation or disappearance) that was found in agreement by both investigators, was recorded. New TMBs (not existing in the initial scan) were searched for on the follow-up images. A similar lesion follow-up approach was performed both on the T1- and T2-weighted images and in the clinical CT scans, but no co-registration was performed for the CT scans.

Approval for the performance of this study was granted by the Institutional Review Board (IRB). Written informed consent was obtained from all the study participants (or their legally authorized representatives).