



Research paper

Microbleeds may expand acutely after traumatic brain injury



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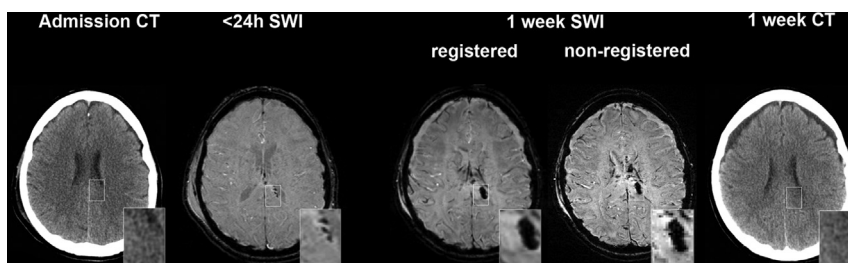
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HIGHLIGHTS

- 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 ≤ 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.
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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 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).

Table 1
Epidemiological, clinical and microbleed parameters.

Patient no.	Age (y)	Gender	GCS ¹	6-month GOS-E	Accompanying non-cranial trauma	EVD ²	Craniectomy	MRI timing		TMB ³ count		TMB volume (voxel)	
								Initial	Second	Initial	Second	Initial	Second (⁴)
1	33	M	6	5	pulmonary contusion	day 1	–	23 h	day 7	26	21	458	684 ($\times 1.49$)
2	36	F	11	7	spinal fracture	–	–	6 h	day 7	14	11	392	1184 ($\times 3.02$)
3	20	M	3	4	sacral fracture multiple maxillofacial fracture	day 1	day 3	20 h	day 8	55	55	4355	4580 ($\times 1.051$)
4	37	M	13	8	pulmonary contusion	–	–	18 h	day 8	5	5	176	160 ($\times 0.909$)
5	49	M	8	8	multiple maxillofacial fracture	day 1	–	6 h	day 9	0	0	0	0

¹ GCS at admission.² External ventricular drain.³ Traumatic microbleed.⁴ volume change ratio between initial and second time point.**Table 2**
MRI protocol technical details.

MRI scanner	Magnetom TIM Trio 3 Tesla (Siemens, Erlangen, Germany)		
Coil	12-channel standard head coil		
Sequence	3D gradient echo SWI ⁵	T1 3D MPRAGE ⁶	T2 turbo spin echo
TR ¹ /TE ² (ms)	27/20	1900/3,41	6000/93
TI ³ (ms)	n.a.	900	n.a.
Slice number	72	160	30
Slice plane	Axial	Axial	Sagittal
Slice thickness (mm)	1.5	0.94	4
Flip angle (degrees)	15	9	120
Matrix size	182 $\times$ 256	224 $\times$ 256	280 $\times$ 320
FOV ⁴ (mm ²)	173 $\times$ 230	210 $\times$ 240	193 $\times$ 220
Receiver bandwidth (Hz/pixel)	120	180	220

¹ Repetition time.² Echo time.³ Inversion time.⁴ Field of view.⁵ Susceptibility weighted imaging.⁶ Magnetization-prepared rapid gradient-echo.

3. Results

TMBs were found in 4 of the 5 patients (patients 1–4). Obvious TMB growth and/or confluence between the two imaging time-points were observed in three patients (patients 1–3, see Fig. 1). These were found in the splenium of the corpus callosum, the coronal radiation, or the subcortical white matter. Novel TMB formation (the appearance of a TMB at a previously unaffected site) or the disappearance of a TMB was not detected between the imaging time points. TMBs without any apparent change were also seen in all four patients who displayed TMBs (see Fig. 2).

The overall TMB number was unchanged (patients 3, 4 and 5) or decreased due to confluence (patients 1 and 2) over time. The overall TMB volume increased substantially in patients 1 and 2 (1.5 and 3-fold increase, respectively), while it changed only slightly in patients 3 and 4 (1.05 and 0.9-fold change, respectively). The overall TMB counts and volumes are shown in Table 1.

Although some TMBs were associated with slight T1 or T2 signal intensity alterations, the comparison of the different time-point T1- or T2-weighted scans did not reveal lesion changes. Similarly, small hemorrhagic lesions (if present at all) on the clinical CT scans did not show progression over time.

The intra- and the inter-rater intraclass correlation coefficients for both the single and the average measurements of the overall TMB volumes exceeded 0.98.

4. Discussion

The findings reported here demonstrate that the SWI TMB appearance may change in the acute phase after injury. The TMBs did not appear or disappear over time, but a proportion of the ini-

tially existing ones underwent an apparent expansion. This was manifested in considerable changes in both the overall TMB count and volume. CT, T1 and T2 MRI failed to detect this expansion. Although it is yet not possible to estimate the rate of occurrence of the TMB expansion in TBI because of the small sample size, the phenomenon itself has both important scientific and practical implications.

The most important practical implication is that scan timing may be a substantial factor when the severity or outcome of DAI is assessed on the basis of TMB parameters such as overall count and volume. In two of the four patients with TMBs, the follow-up imaging showed fewer TMBs, but their overall volume had become obviously higher (1.5 and 3-fold increase) due to the expansion and confluence. Neither the number nor the volume of the TMBs can therefore be regarded as a constant marker in the acute phase after TBI. Either the optimal imaging time point should be described, i.e. the time after injury when the possibility of TMB alteration drops significantly, or SWI should be used as a tool for follow-up. Whereas recent studies have shown impressive relations between the single SWI findings taken at inconsistent time points and the clinical factors [2,25,33], it is quite likely that these results would have been improved if consistent multi-time point imaging protocols had been applied. We agree with the conclusion of previous investigations of long-term microbleed changes [20,22] that imaging in TBI should not be performed too late because TMBs may undergo an attenuation. However, too early single time point imaging might also be disadvantageous if a TMB expansion is then missed.

An explanation of the pathological background might be that microvascular damage underlying DAI-related microbleeds is not complete in the very initial period after injury –similar to DAI itself, which is known to constitute a complex degradation process reaching its maximum in a delayed fashion after injury [6].

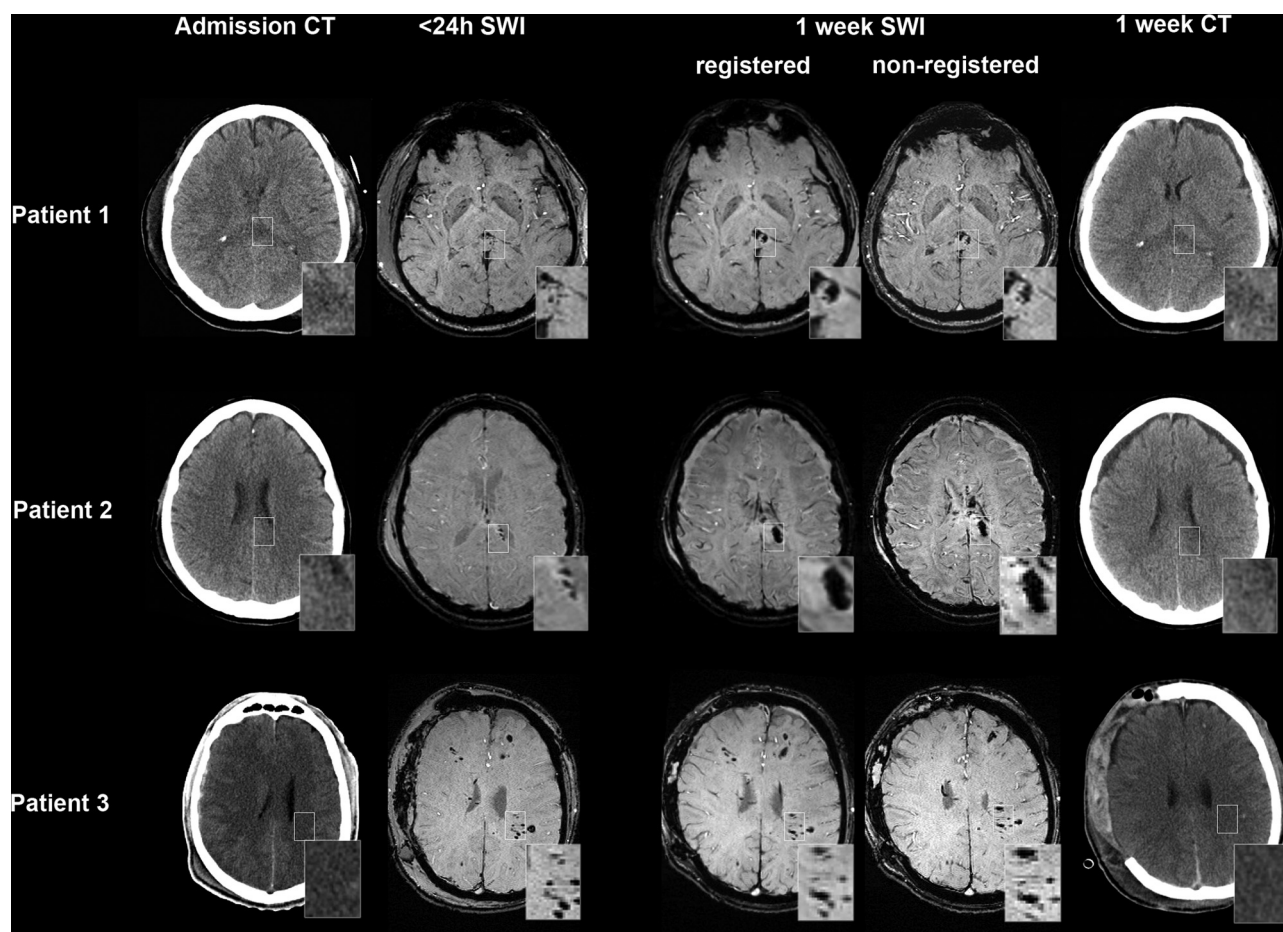


Fig. 1. TMB growth and confluence examples in the first week after TBI.

This figure shows the initial (<24 h) and the follow-up (1 week) CT and SWI scans of patients 1–3. The inserts show identical anatomical locations in the co-registered initial and follow-up SWI scans, and the possible closest anatomical slice in the CTs and non-registered follow-up SWI scans per patient.

In patient 1, multiple TMBs can be seen in the left side of the splenium of the corpus callosum which underwent growth and confluence (has become one larger TMB on follow-up SWI).

Patient 2 presents a very similar TMB change in the left side of the splenium.

In patient 3, the growth of two TMBs in the left posterior coronal radiation can be seen. The hypointensity that appeared in the anterior left hemisphere in the follow up SWI scan is a result of the insertion of an external ventricular drain, following the initial imaging time point.

These microbleeds and changes are not detectable in the admission or follow-up CT scans either.

An argument against this is that microbleed expansion was not general in our patients, but was limited to certain foci. It is possible that these locations were prone to minor shear-strain effects linked to inter-compartmental brain shifts caused by brain edema progression/regression. These forces seem to be large enough to cause recurrent bleeding in the already damaged capillaries.

A long-term follow-up study on stroke patients related blood pressure variability to microbleed progression [19]. Although the investigated time-span and the background pathology were very different, blood pressure variations might play a role in the post-traumatic acute microbleed expansion too. A further theoretical explanation for the focal microbleed expansion might be possible variations in perfusion rate in the different brain regions [12]. Further studies in which MR perfusion techniques are combined with SWI might reveal such mechanisms.

None of the patients received anticoagulant therapy prior to trauma, though due to general neuroanesthetic protocols [26], the severe TBI patients (patients 1, 3 and 5) received preventive-dose low-molecular-weight-heparin within 24 h after injury. Theoretically, this might have facilitated microbleed evolution, but it is definitely not strictly linked to it, since one low-molecular-weight-heparin receiver (patient 5) did not display TMB evolution at all, while non-anticoagulated patient 2 presented an apparent TMB

expansion. If post-traumatic anticoagulant therapy is related to microbleed expansion at any rate, follow-up SWI should be proposed as a potential tool to assess patient safety besides the currently used CT protocols.

Since other imaging methods are less sensitive in detecting microbleeds [3,7], and histological investigations do not allow intra-subject follow-up, SWI appears to be the best tool for investigation of the pathomechanism of TMB progression.

Hemoglobin degradation products are well known to have substantially different T1 or T2 contrasts [23]. Moreover, it must be borne in mind that because of the blooming (susceptibility) effect, the microbleeds are actually considerably smaller than appears on the T2* or SWI images [11]. In theory, therefore, hemoglobin degradation could result in an altered susceptibility effect that might cause a pseudo-change in the size of the microbleeds, i.e. not their true size, but their susceptibility effect could change due to hemoglobin degradation. The literature regarding this question is surprisingly scarce. Two previous studies have investigated the acute evolution (from hours to weeks) of an experimental intracerebral hemorrhage in rats, in which not only T1- or T2-weighted imaging, but also SWI was applied [4,17]. The overall diameter of the intracerebral hematoma gradually decreased over time in both studies. However, again in both studies, the signal intensity

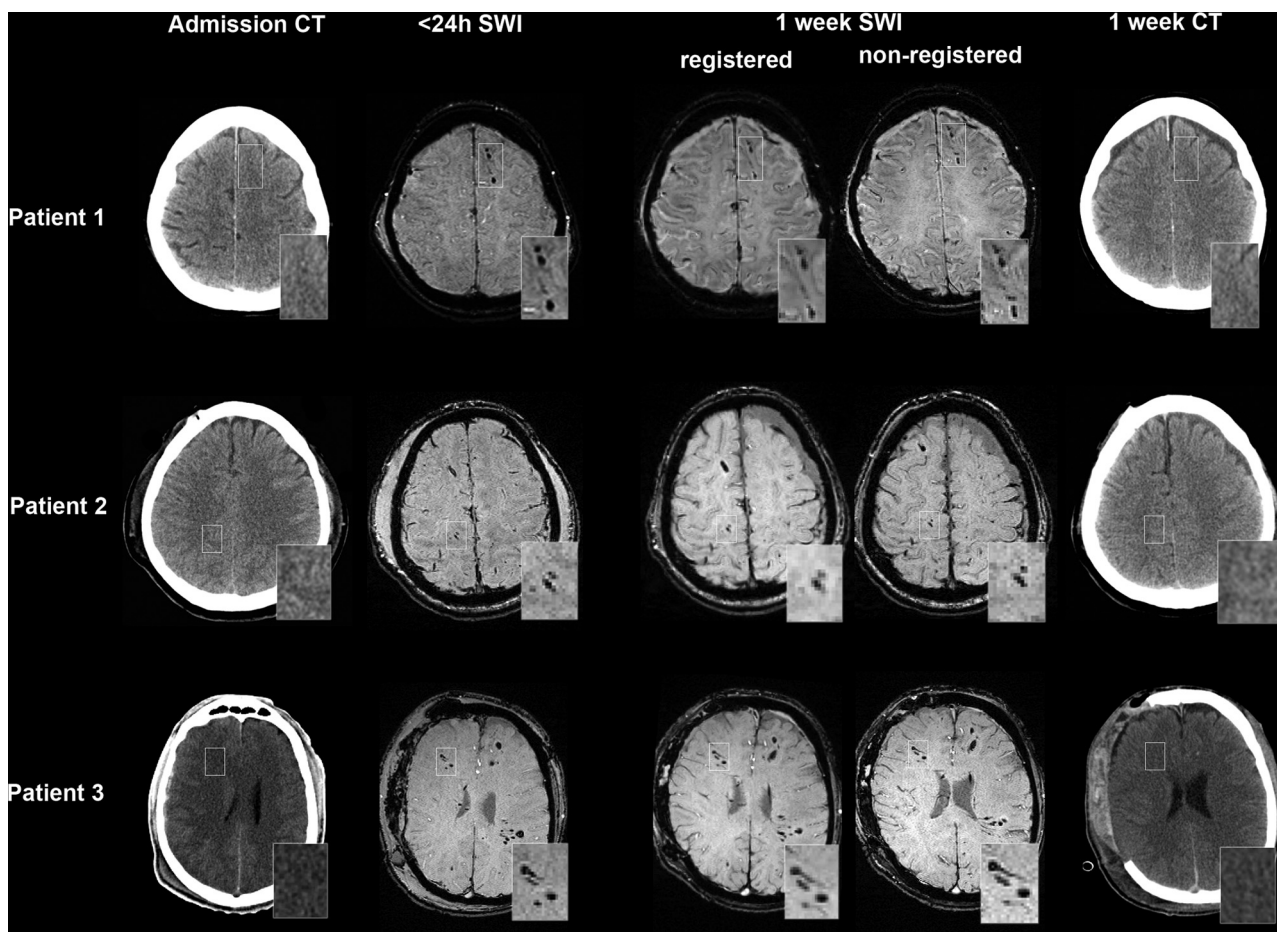


Fig. 2. Non-changing TMBs from the same patients (patient 1–3) in the first week after TBI.

This figure shows the initial (<24 h) and the follow-up (1 week) CT and SWI scans of patients 1–3. The inserts show identical anatomical locations in the co-registered initial and the follow-up SWI scans, and the possible closest anatomical location in the CTs and non-registered follow-up SWI scans per patient.

reversed (it became hyperintense) in the core area of the intracranial hematoma after 24 h. The volume of this central hyperintensity then decreased, but was still visible at 1–2 weeks. The authors suggested that this hyperintensity was due to the presence of extracellular methemoglobin [17]. These studies therefore support the view that hemoglobin degradation indeed affects the susceptibility effect. Theoretically, the reappearance of susceptibility during the cessation of hyperintensity could result in a false impression of microbleed expansion. However, this mechanism is very unlikely to explain the demonstrated microbleed changes in the present study if the following points are considered: A. The overall diameter of the expanding lesions increased over time even when all the pre-confluence microbleeds were taken into account. B. A slight hyperintensity, if present at all, is located not centrally, but “rim-like”, related to the hypointensities, and is visible at the 1-week acquisition rather than at 24 h. C. In humans, extracellular methemoglobin is known to appear first only after 7 days and thus the related hyperintensity would cause a false appearance of shrinkage, and not expansion, between 24 h and 7 days. D. Non-changing TMBs beside the expanding ones within the same patients indicate that lesion expansion is not general, as it should be if it were caused by hemoglobin degradation.

Unfortunately, the data available at present are insufficient to assess the clinical significance of microbleed expansion: though clinical variables such as GCS and GOS-E score were recorded, the statistical testing of their correlations with microbleed expansion would have required a larger sample size, especially if corrections for epidemiological factors had been performed. Following a non-

statistical evaluation of the data, the initial GCS does not appear to be strictly correlated with microbleed progression, since it occurred in patients with GCS levels of 3 and 11. However, we hypothesize that microbleed expansion is related to clinical deterioration, especially when eloquent brain areas or associated tracts are affected. This may only be recognized as a poorer final outcome in the comatose or anesthetized patients.

In the present study, we adhered to very strict inclusion and exclusion criteria in order to rule out as much as possible the potential disturbing effects of non-traumatic microbleeds. Non-traumatic microbleeds are associated with aging [24], vascular diseases (including diabetes, smoking and uncontrolled hypertension) and several central nervous system disorders [11,21]. This resulted in a high number of excluded patients. Patient movement in the post-traumatic phase is often unsafe, making noncompulsory study MRIs impossible. A very early MRI in moderate to severe TBI has especially high infrastructural and personnel requirements. These factors together explain the small sample size of this study. However, this study is intended to present a previously unrecognized phenomenon, the possible expansion of TMBs. Further studies based on larger samples should reveal the epidemiological background or the clinical correlations of acute TMB expansion.

5. Conclusion

In conclusion, this study has shown that the development of microbleeds is not limited to the moment of injury, but a proportion of them may undergo an apparent expansion in the subsequent

days. This affects both the overall microbleed count and volume. Scan timing may therefore be a crucial factor when the severity or outcome of DAI is assessed on the basis of SWI-detected TMB parameters.

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