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Susceptibility-Weighted MRI in Mild Traumatic Brain Injury: the Importance of Cerebral Microbleeds

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Abstract

Mild traumatic brain injury (mTBI) is a large subgroup of traumatic brain injury in which patients experience minor but persistent neurophysiologic dysfunctions that lead to disability in social interaction and daily work. New emerging magnetic resonance imaging (MRI) techniques hope to provide better understanding of the underlying pathophysiology of various symptoms in mTBI. Susceptibility-weighted MRI (SWMRI) is a MRI technique particularly sensitive in detecting cerebral microbleeds (CMBs) in the brain parenchyma. Studies have shown evidence of CMBs associated with mTBI, particularly at gray-white matter junction. Although the significance of CMBs has been debated in recent years, there are evidences that these subtle image findings may have diagnostic and prognostic implications, and possibly an imaging biomarker in mTBI. SWMRI is recommended as complementary sequence to the MRI protocol for patients with mTBI for detection of CMBs as well as for further evaluate the severity of injury and future treatment planning.

Introduction

Traumatic Brain Injury (TBI) is the most common worldwide neurologic condition, with an incidence of 235-556/100000, and more than 75% of TBIs are classified as mild traumatic brain injury (mTBI) by definition of the American Congress of Rehabilitative Medicine [1-3]. By definition, a patient of mTBI is a person who has had a traumatically induced physiological disruption of brain function, but where the severity of the injury does not exceed the following: loss of consciousness (LOC) of approximately 30 minutes or less, Glasgow Coma Scale (GCS) score of 13 to15 upon acute medical evaluation, and post-traumatic amnesia (PTA) less than 24 hours in duration [4]. Common causes of mTBI are traffic accident, accidental falls, and sports-related repetitive concussive head trauma, such as in boxing, hockey, and football [5-7]. Despite the lack of evident pathologic abnormalities on conventional neuroradiological examinations, nearly a third of mTBI patients develop less severe but persistent neurophysiologic dysfunctions, such as headache, nausea, dizziness, inability to concentrate, irritability, memory impairment, cognitive decline, personality changes, and generalized fatigue. The course is usually self-limited, resolving within 6-8 weeks in 85-90% of patients, but some may persist for life, leading to disability in social interaction and daily work [8].

To date, there is a lack of effective clinical, laboratory, or image makers as prognostic factors for patients of mTBI. Previously considered a temporary disruption, there have been several different approaches in attempt to understand the pathophysiology of various symptoms in mTBI. Performance in neuropsychological tests has been applied to investigate the severity of the symptoms and clinical relevance. Neuroradiology examinations were used to identify the possibly structural changes in the brain parenchyma. The standard method for primary survey of head trauma is computed tomography (CT) due to its accessibility and short scan time. Magnetic Resonance Imaging (MRI) is preferred for further investigation in subacute to chronic phase for subtle intraparenchymal lesions and edema. However, results of CT and routine MRI scans nearly always reveal negative or equivocal findings for patients of mTBI.

Susceptibility-Weighted MR Imaging

Susceptibility-weighted MRI (SWMRI) has been increasingly used in neurology and cerebrovascular research for visualization of the venous vasculature and detection of cerebral microbleeds (CMBs). It is an imaging technique that was developed in 2004 by Haacke et al. using the basic physical phenomenon of paramagnetic elements [9]. As a paramagnetic element, iron has different magnetic susceptibilities to the surrounding parenchyma, and it changes the local magnetic field in the presence of an externally applied magnetic field. SWMRI is a modified high spatial resolution T2-weighted 3D gradient recalled-echo (GRE) MR technique that accentuates the magnetic properties of blood products, improving detection of small amounts of paramagnetic hemorrhagic blood products, extravascular deoxyhemoglobin and methemoglobin, based on the susceptibility difference between blood products and the surrounding brain tissue. SWMRI have shown greater sensitivity and accuracy in detecting traumatic-related injuries, such as diffuse axonal and vascular injuries, than CT and conventional MR techniques [10-13]. The two most common SWMRI in clinical use are susceptibility-weighted imaging (SWI) and susceptibility-weighted angiography (SWAN), both have similar ability in the detection of CMBs, and are superior to traditional T2*-weighted GRE in both detection rate and spatial resolution. Furthermore, much smaller voxel size of SWMRI enables the detection of smaller CMBs, whereas the combination of increased echo time and decreased bandwidth and flip angle ensures a high signal-to-noise ratio and adequate contrast between CMBs and surrounding brain tissues [14-16].

Currently, CMBs are most commonly defined as SWMRI hypointense lesions less than 5mm in diameter and match the

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following recommended criteria: black on T2*-weighted MR imaging, round or void, blooming on T2*-weighted MR imaging, devoid of signal hyperintensity on T1- or T2-weighted sequences, at least half surrounded by brain parenchyma, and distinct from other potential mimics such as iron/calcium deposition, bone, or vessel flow voids [17] (Figure 1). Common causes of CMBs are hypertensive vascular disease, lacunar infarction, cerebral amyloid angiopathy, and traumatic-related micro hemorrhages. Less common causes include cerebral embolism, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), multiple cavernous malformations, vasculitis, hemorrhagic micro metastasis, radiation vasculopathy, and Parry-Romberg syndrome [18].

Histopathology and neuroimaging correlation of cerebral microbleeds

Pathologically, CMBs are composed of accumulation of hemosiderin-containing macrophages following a micro hemorrhage [19]. In clinical setting, however, the diagnosis of CMBs is primarily based on image findings. Exactly how reliable are these MRI-detected CMBs? Histopathological confirmation of CMBs seen on neuroimaging is important because there are a number of CMB mimics, such as vascular micro calcification, micro aneurysm, and contained erythrocytes. To date, there has not been any report of histopathology-neuroimaging correlation of mTBI-related CMBs. However, studies in which CMBs were characterized histopathologically and correlated with MRI (both antemortem and postmortem) in patients of cerebrovascular diseases have shown credibility of these MRI-detected CMBs (Figure 2).

A literature review by Shoamanesh et al. suggested a strong association between MRI-detected CMBs and histopathological evidence of previous hemorrhage [20]. The result of 85 MRI-detected CMBs from 18 patients showed corresponding histopathology findings of hemosiderin and iron depositions in 68% of the CMBs, 15% showed no specific pathology, 13% contained intact erythrocytes, and the remaining 3% showed vascular psuedocalcifications, microaneurysms, and distended dissected vessels. A study by De Reuck et al. investigated CMBs on postmortem brain sections from Alzheimer patients using 7-tesla MRI showed the sensitivity and specificity of 7-tesla MRI imaging to be 100% and 50%, respectively, for detecting CMBs of 1-3 mm diameter and 100% and 38%, respectively, for smaller hemorrhages of 200-500 μm [21].

The accuracy of the CMB sizes is debatable. In a study by Schrag et al., the CMBs were 1.57 ± 0.75 times larger than their corresponding lesion on pathology due to 'blooming effect', and noticed that the magnitude of 'blooming' was greater for smaller lesions [22]. In contrast, Tatsumi et al. reported the actual sizes of the CMBs are comparable with those detected on MRI [19]. One should keep in mind that the size of MRI-detected CMBs can vary with the change of imaging parameters (TR/TE, slice thickness, flip angle) [19,20]. Lengthening the TE or decreasing the flip angle is known to increase the size of CMBs. The 'blooming effect' of MRI can overestimate the diameter of a CMB.

Application of susceptibility-weighted imaging in mild traumatic brain injury

In recent years, there has been an exponentially growing interest and debate in determining the clinical significance of CMBs in association with mTBI. Three main concerns were discussed in the previous studies.

Significant presence of CMBs in mTBI patients

All most all earlier studies showed no evident prevalence of CMBs in mTBI patients, however, these earlier studies were mostly using CT, 0.5-Tesla MR scanner, or conventional MR Sequences [23-26]. Two studies by Hahnel et al. and Hasiloglu et al. both used GRE MRI to detection of CMBs in amateur boxers in comparison with healthy non-boxing volunteers (3T GRE and 1.5T SWI, respectively) [5,6]. Both studies showed similar results with more CMBs detected in amateur boxers (42 and 21 respectively) than control (37and 21 respectively), but the difference did not prove to be significant. A recent large group study by Huang et al., with 111 subjects in both mTBI and control groups, showed the prevalence of CMBs in mTBI patients was 23.4%. Furthermore, in comparing to healthy volunteers, nearly 4 times as many microbleeds identified in mTBI group than in control group (60 and 15, respectively). This is by far the study with largest number of subjects, and their analysis between the two groups should demonstrate a certain level of statistical reliability [27].

The location of the CMBs in mTBI

Nearly all studies have shown consistency of most mTBI-related CMBs to be located at gray-white matter junction (Figure 3). Although the result by Hasiloglu et al. in amateur boxers was not statistically significant, their results showed that all CMBs were located exclusively in the corticomedullary junction of frontal and temporal lobes [6]. The study by Huang et al. also showed significantly more CMBs at corticomedullary junction than in controls (86.7% vs. 20%) [27]. This owes to the pathophysiology associated with mTBI. Torsional forces during traumatic brain injury generated by rapid acceleration or deceleration of the head cause the shearing of axons, resulting in diffuse axonal injury (DAI). The acceleration shearing force on axons is often

Recommended Criteria for CMB on MRI

1. Black on T2*-weighted MRI
2. Round or ovoid (rather than linear)
3. Blooming on T2*-weighted MRI
4. Devoid of signal hyperintensity on T1- or T2-weighted sequences
5. At least half surrounded by brain parenchyma
6. Distinct from other potential mimics, such as iron/calcium deposition, bone, or vessel flow voids

Figure 1: Recommend criteria for CMB identification on MRI by Greenberg et al. [17].

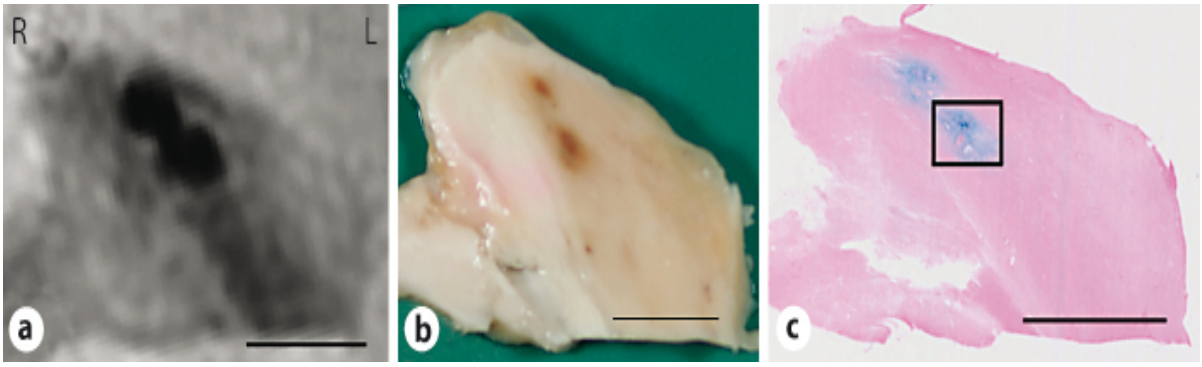

Figure 2: Histopathology-neuroimaging correlation of CMBs. Two CMBs of the right thalamus. **(a)** Postmortem GRE-MRI. **(b)** Macroscopic appearance (brown spots). **(c)** Iron stain (blue lesions). These CMBs are roughly similar in size in each picture. Scale bar = 10mm. (From Direct Comparison of Histology of Microbleeds with Postmortem MR Images. Cerebrovasc Dis 26:142-146; with permission)

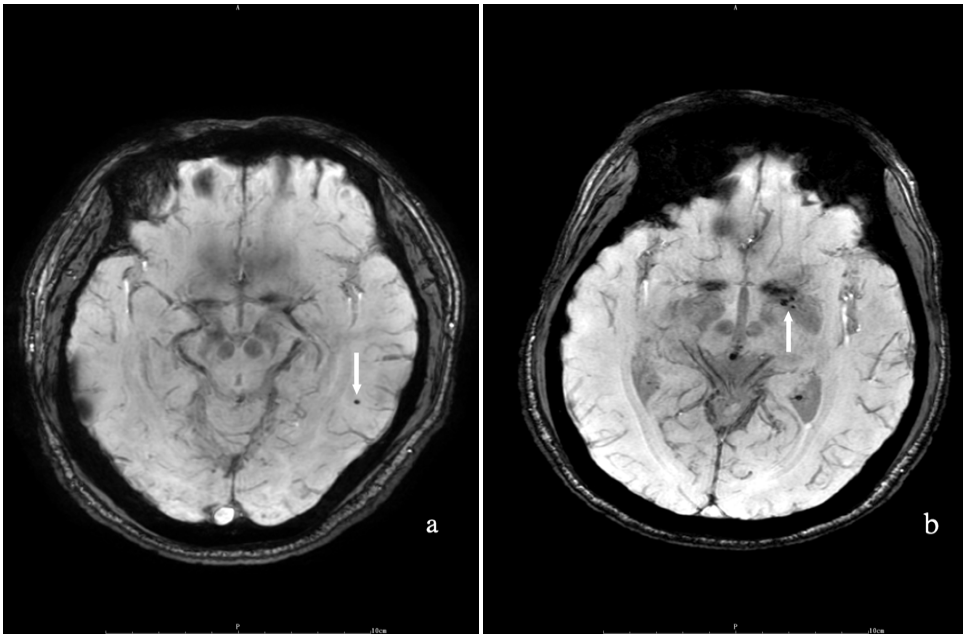

Figure 3: SWMRI imaging of CMBs.
(a) Axial SWAN images depicting CMBs at corticomedullary in an mTBI patient. (b) In contrasts, CMBs associated with hypertensive vascular disease are often located at deep gray matter.

accompanied by petechial tissue-tear micro hemorrhages due to injury of vascular endothelium, leading to extravasation of blood products that are not routinely visible on CT or conventional MRI sequences, but more apparent on T2*-weighted MRI than on conventional MR sequences [28,29]. Areas most vulnerable to shear injury include the cerebral gray-white matter (corticomedullary) junction, splenium of the corpus callosum, and dorsolateral brainstem [18]. Thus, the location of mTBI-related CMBs detected on MRI is consistent with pathophysiological findings.

Clinical significance of CMBs in mTBI

There has been a growing interest in determining whether these SWMRI-detected CMBs contribute to clinical neurological dysfunctions. Park et al. noticed that there seems to have positive relationship between location of CMBs and specific symptoms. For example, CMBs at occipital lobe, pons, and midbrain seemed to be accompanied with visual field defect, sensorineural hearing loss, and Parkinson syndrome, respectively [10]. Huang et al. compared neuropsychological tests between mTBI patients with SWMRI-detected CMBs and those without. Those with CMBs had significantly lower digit span score, a test focusing on short-term memory, than the patients without CMBs [27]. The results indicated that those with mTBI-related CMBs showed neuropsychological defect on short-term memory function.

Though the evidences are still insufficient, but they suggested that CMBs could be a possible biomarker for mTBI. However, it should be reminded that CMBs themselves do no cause change in neuropsychological performance; rather, they are an epiphenomenon of underlying injury to neuron and vascular tissues. Further correlation of SWMRI-detected CMBs with other functional MRI is required for further understanding of the pathophysiology and alteration in neuroconnectivity.

Conclusion

Once thought to be an irrelevant finding, these subtle mTBI-related CMBs are now shown to have diagnostic and prognostic implications and a possible imaging biomarker in mTBI. SWMRI is recommended as complementary sequence to the MRI protocol for patients with mTBI for detection of CMBs and to further evaluate the severity of injury and future treatment planning. Furthermore, the SWMRI-detected CMBs are merely the "tip of the iceberg" of underlying DAI. Other emerging functional MR techniques, such as DTI, have been explored for further evaluation of the connectivity defects from DAI that may be associated with clinical neuropsychological dysfunctions.

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