Commentary

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Brain tissue iron quantification by MRI in intracerebral hemorrhage: Current translational evidence and pitfalls

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Abstract

Intracerebral hemorrhage (ICH) is a common subtype of hemorrhagic stroke with devastating consequences with no specific treatment. There is, however, substantial evidence for iron-mediated neurotoxicity in animal ICH models. Non-invasive quantification of the peri-hematomal tissue iron based on MRI has shown some promise in animal models and is being validated for clinical translation. This commentary reviews evidence for this approach and discusses potential pitfalls.

Keywords

Iron quantification, MRI, ICH, hemoglobin, translation

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Introduction

Intracerebral hemorrhage (ICH) is a devastating subtype of stroke with high mortality and morbidity. After an ICH, there is physical disruption to the brain (primary injury) but also delayed, secondary, injury.[1] Clot-derived factors, including hemoglobin and iron, have been implicated in having a major role in such secondary injury.[1] This has led to a phase-I[2] and now a phase-II trial (iDEF; NCT02175225) examining an iron chelator to reduce ICH-induced brain injury. A non-invasive method, such as MRI, that could quantify hematomal and peri-hematomal iron concentrations in animals and patients would be a great asset in such studies. It might allow: (a) assessment of hematomal changes with time; (b) quantification of iron at different distances from the hematoma with time; (c) animal and human studies could be compared, facilitating translation; (d) iron chelator target engagement could be assessed; (e) interpatient variability (e.g. in the rate of hematoma iron release) could be examined. This has led investigators, including the current authors, to examine using T2* MRI to examine changes in iron after ICH.[3,4] This commentary discusses the associated nuances and potential pitfalls that will influence interpretation of such MRI images.

Imaging characteristics of a hematoma on MRI

There is a standard understanding about changes in T2* signal on MRI in an ICH, where four phases have been described: Hyperacute, Acute, Early and Late Subacute, and Chronic. While the changes in T1 and T2 weighted sequences is defined, changes on T2* sequences are not. In the hyperacute stage, signal hypointensity on T2* sequences, is understood to be due to oxyhemoglobin within the hematoma.[5] However, animal and human hematomas on T2* MRI can appear inhomogeneous[6] and a phenomenon of ultra-early erythrolysis has been demonstrated on histology in preclinical ICH models.[7] This phenomenon

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of ghost erythrocytes, devoid of hemoglobin within the hematoma was found within 24 hours of hematoma formation. The authors conducted an experiment to define this further. Vials with different concentrations of lysed and unlysed porcine blood (100, 75, 50, 25 and 0%) were created by rapid freezing and thawing prior to T2* MRI. As the portion of lysed blood increased, the T2* signal intensity increased with a bright signal on the 100% lysed portion (unpublished work). This experiment shows that within the hematoma, the extracellular, lysed RBC hemoglobin exhibits less T2* susceptibility shortening relative to unlysed RBC. As diffusing water protons traverse steep susceptibility gradients over interval TE (time to echo), a greater degree of T2* signal is lost for the intracellular hemoglobin, whereas T2* signal persists for lysed RBC state. All the hemoglobin within a hematoma is not necessarily intracellular and a large proportion of extracellular hemoglobin can cause a T2* non-hypointensity on MRI. Thus, the phenomenon of T2* signal non-hypointensity may not be all explained by oxyhemoglobin, but more so by the proportion of intra or extracellular hemoglobin affecting T2* signal intensity. The authors are currently studying this phenomenon of ultra-early erythrolysis in humans.

Peri-hematomal iron quantification techniques on MRI

With time after ICH, hemoglobin, in its intra or extracellular form starts causing signal hypointensity on T2* sequences based on its susceptibility to cause signal inhomogeneity. Deoxygenated hemoglobin has a greater paramagnetic effect than oxygenated hemoglobin. Hemoglobin in its deoxygenated form exposes more iron molecules to cause signal distortion on MR sequences. This ability of iron to cause signal distortion and field inhomogeneity can be quantified by MRI to assess peri-hematomal iron concentration.[3,4] MRI-based peri-hematomal iron concentrations correlate very well with macroscopic iron quantification determined upon animal euthanasia. However, the susceptibility from iron within the hematoma is very strong making iron quantification currently impossible. When extrapolating signal magnitude to iron concentration, the susceptibility sequence applied and the region of interest application has to be chosen appropriately. The authors advocate for a multiple echo train length when applying the PADRE (Phase Difference Enhanced) MRI sequence to measure phase difference from iron in brain tissue. The data collected over 8 to 16 echo points from the initial applied radio frequency pulse, to create T2*/R2* maps, is a more robust scientific technique. As shown by the studies described, there is a near linear correlation of T2* signal with iron concentration if Relaxivity maps ($R2^* = 1/T2^*$) are applied ideally on a 3Tesla (or greater) MR scanner. It is not certain whether amongst other sequences like QSM (quantitative susceptibility mapping) and DWI, employed in detection of iron in ICH, there is a clear winner.[8,9] Future human translational studies should apply the above rigor when assessing peri-hematomal iron concentrations in ICH.

The authors also recommend internal validation with measurements of iron-mediated signal phase difference on the contralateral identical anatomical site. This maneuver will normalize the measurements on the side of the hematoma. Most studies have performed ipsilateral measurements to the hematoma.

An unknown factor that deserves investigation is the impact of different iron chelators on T2* signals. For example, does ferritin vs. hemoglobin iron binding change its paramagnetic properties? Further studies with MR markers attached to these molecules may shed more light on the different forms of iron attached to different iron handling molecules and its related signal alteration on MRI.

Future directions

The scientific community eagerly awaits the results of the recently concluded MISTIE III trial on hematoma evacuation and the iDEF trial on iron chelation for ICH.[10] In such studies, a validated MRI-based iron quantification technique could be applied as a temporal objective marker of peri-hematomal tissue iron levels, apart from potentially becoming a risk stratifying marker. In addition, such a technique would provide an important experimental and clinical tool for studies on subarachnoid and intraventricular hemorrhage.

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