Iron-Enhanced MRI in Ischemic Stroke: Intravascular Trapping Versus Cellular Inflammation

To the Editor:

With great interest we read the article by Wiart et al on the application of ultrasmall superparamagnetic iron oxide particles (USPIO) as MR contrast medium in experimental stroke. Iron particles were administered 5 hours after permanent occlusion of the middle cerebral artery (pMCAO). Subsequent MRI investigations were performed from 6 to 72 hours after pMCAO. Already 6 hours after pMCAO and 1 hour after iron particle injection a hypointense rim surrounding the ischemic lesion was present indicating focal iron deposition. This rim-like signal loss persisted until 72 hours post-pMCAO. Surprisingly, on histology at 24 hours only few F4/80-positive cells were found in the vicinity of the lesion, whereas at 48 and 72 hours a larger number of these cells was present. The authors consider the diffusion of iron particles through the disrupted blood-brain barrier with subsequent uptake by activated microglia as the most likely explanation for the observed signal loss on MRI at the early stages of infarct development which apparently did not match to the extent of inflammation.

We have recently shown in a rat model of cerebral ischemia that intravascular iron particles are trapped in developing thrombi which also appear as signal loss on MRI. When iron particles were applied during the induction of ischemic stroke, the infarct core reveals a signal loss; delayed application within hours after induction of ischemia results in a hypointense rim surrounding the lesion. This is caused by ongoing thrombus formation and infarct growth at the periphery with trapping of iron particles. At these early stages local iron accumulation is not related to the presence of inflammatory cells. When the same animals, however, are followed for days, finally iron particles are also found within macrophages/microglia that clear tissue debris including occluded vessels and their locally trapped iron particles. Thus, our findings are in line with the observations by Wiart et al who found increasing numbers of iron-laden F4/80-positive phagocytes from day 2 on after ischemia.

As the authors stated in the discussion, neuroinflammation after stroke is considered to be a delayed event. By using iron-enhanced MRI we could show that blood-borne macrophages start infiltrating the periphery of ischemic lesions around day 6. Similar results were obtained in human stroke. At day 8, signal loss was restricted to the inner core and ceased thereafter. This iron-induced signal loss indicated active macrophage transmigration into ischemic infarcts.

In conclusion, 2 distinct mechanisms of local iron accumulation after ischemic stroke must be considered: at early stages (within hours) signal loss may mainly be caused by intravascular trapping of iron particles within developing thrombi, whereas at later stages (within days) it is attributable to macrophage infiltration. It appears that the signal loss observed early after MCAO in the border zones of the lesions in the study by Wiart and colleagues similarly reflects ongoing thrombotic vessel occlusion with intravascular trapping of iron particles rather than neuroinflammation or unspecific leakage/uptake of iron particles. Unspecific iron leakage was never observed in our study using iron particles despite early breakdown of the blood-brain barrier as highlighted by gadolinium-DTPA enhancement.

Disclosures

None.

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