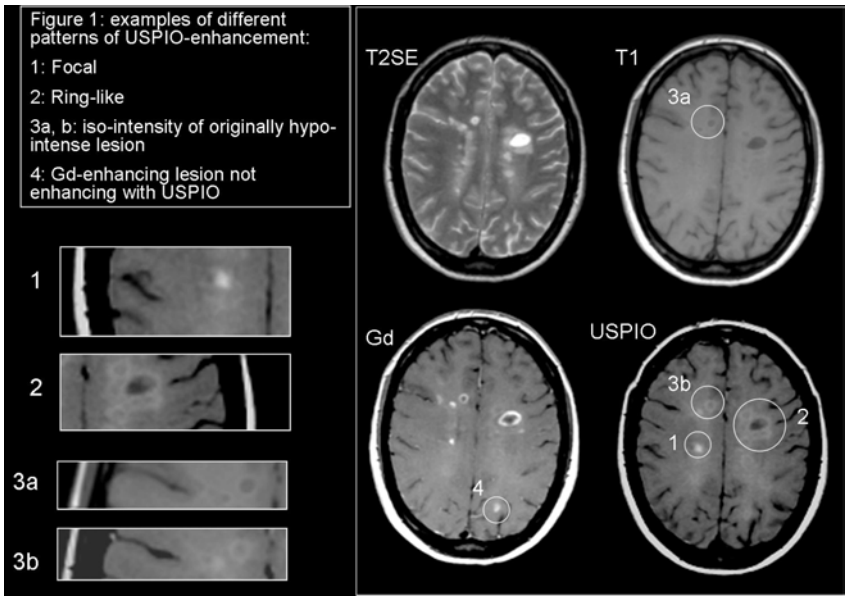
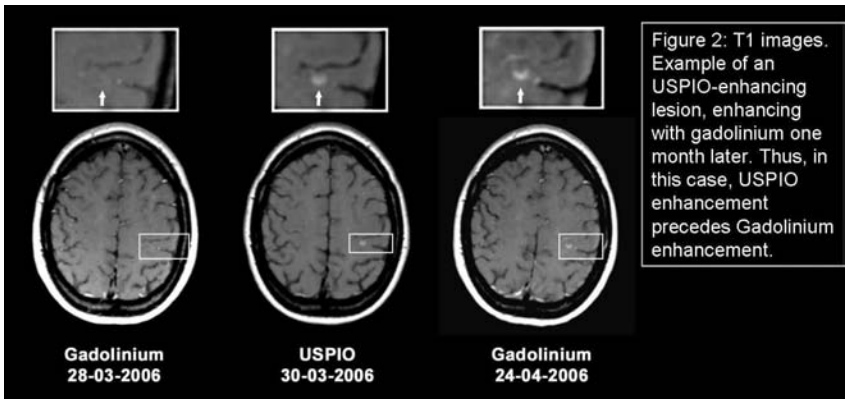
USPIO-enhanced cellular imaging in MS

M. M. Vellinga[1], J. J. Geurts[2], S. M. van der Pol[3], C. Pering[4], C. H. Polman[1], H. E. de Vries[3], and F. Barkhof[2]

[1]Neurology, MS Center Amsterdam, VU University Medical Center, Amsterdam, Netherlands, [2]Radiology, MS Center Amsterdam, VU University Medical Center, Amsterdam, Netherlands, [3]Cell Biology & Immunology, MS Center Amsterdam, VU university Medical Center, Amsterdam, Netherlands, [4]Schering AG, Berlin, Germany

Background: new therapies in Multiple Sclerosis (MS) aim at preventing cellular infiltration into the brain parenchyma. In evaluating therapeutic efficacy, ultrasmall superparamagnetic particles of iron oxide (USPIO), which are taken up by macrophages and are transported into inflammatory MS lesions (1-3), may be a more specific MRI marker than Gadolinium-DTPA (Gd), which merely visualizes breakdown of the blood-brain-barrier.
Objective: to visualize cellular infiltration in MS inflammatory lesions using USPIO in a phase II setting, and to compare it to Gd enhancement.
Patients and Methods: relapsing-remitting MS patients are currently screened monthly, using T1-weighted spin-echo (TR 830 ms; TE 15 ms; slice thickness 4 mm), dual-echo T2-weighted spin-echo (TR 3837 ms; TE 98 ms; slice thickness 4 mm), and T2 gradient-echo (TR 615 ms; TE 27 ms; slice thickness 4 mm). In case of a Gd-enhancing (Gd+) lesion, USPIO (SH U 555 C, Schering AG, Berlin (Germany), diameter: 25 nm, $T_{1/2}$ 6-8h, provided free of charge) are administered (single intravenous bolus injection of 40 micromol Fe/kg BW) within 24-48 hours. Twenty-four hours after injection, MRI is performed (same protocol) and blood is withdrawn to evaluate monocyte activation levels and USPIO-uptake. Follow-up consists of 3 monthly scans. Clinical disability (EDSS) and relapses are registered throughout the study.
Results: so far, 20 patients have been included, 13 of which have received USPIO. Inclusion is ongoing. In our preliminary dataset, USPIO-enhancement (hyperintense on T1) occurred in 4 different patterns (see Figure 1); 1: focal, some with small clusters around original Gd+ lesion; 2: ring-like, sometimes surrounding a Gd+ lesion; 3: as an isointense signal in originally hypointense lesions (on pre-contrast T1); 4: USPIO-enhancement not visible as Gd-enhancement on prior images; some of these lesions were Gd-enhancing at 1 month follow-up (Figure 2). Not all Gd+ lesions showed USPIO enhancement. USPIO labelling of monocytes was successful in vitro as well as in vivo.
Discussion: Surprisingly, no signal changes were observed on the gradient-echo T2. Preliminary in vitro imaging results seemed to indicate a concentration-dependent effect on T1-enhancement. The administered concentration of SH U 555 C in the patients of this study is probably too low to induce a signal decrease on T2*-weighted images. Future studies will include quantification of lesions of the four different enhancement patterns, follow-up of lesion development on MRI, and additional in vitro imaging experiments with labelled monocytes.
Conclusion: USPIO-enhancement is based on infiltration of labelled macrophages into inflammatory lesions, and shows patterns that are distinct from Gd enhancement in MS.These different patterns may reflect different types of pathology.





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