Heterogeneity of brain inflammation following human ischemic stroke: Evidence from USPIO -enhanced MRI

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Introduction

Heterogeneity of stroke is regarded one of the main obstacles for establishing new therapeutic approaches. New methods are demanded to get additional *in vivo* pathophysiological information to tailor stroke therapy more individually.

Focal cerebral ischemia elicits a profound inflammatory response which is a potential therapeutic target in subacute stroke. Ultrasmall particles of iron oxide (USPIO)-enhanced MRI has visualized macrophage influx in experimental stroke (1,3,5). Recently, we visualized brain inflammation in human stroke at the time of maximum hematogenous macrophage influx, i.e. one week after ischemia onset (4). Extending our earlier experimental studies we now asked whether USPIO enhancement can be detected in the early phase after stroke..

Methods

Patients

This study was approved by the local ethics committee. An initial Stroke-MRI(fig.1) was done within 24 hours after symptom onset, and patients without evidence of hemorrhage were included. Accordingly, the first USPIO-enhanced MRI was obtained 3-4 days after ischemia onset. This reports on the first 12 patients enrolled in this ongoing study.

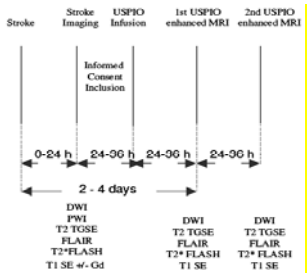


Fig.1 displays the study protocol.

USPIO

Ferumoxtran (Sinerem®) was kindly provided by Guerbet (Roissy CDG Cedex, France), reconstituted due to the manufactures instructions. It was administered in a single dose infusion (2,6mg iron/kg body weight) through a 0,22µm pore filter at a rate of 4ml/min. Post infusion scan was timed 24-36 and 48-72 hours USPIO infusion. We observed no adverse effects.

MRI acquisition

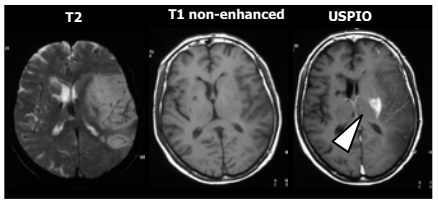
MRI was done on a 1,5T Siemens Vision Scanner. Infarcts were clearly outlined by diffusion-weighted(DWI) and T2-weighted images. As known from the former study(4), most pronounced USPIO effects were seen at best in the T1 images. We therefore demonstrate USPIO-related effects on T1 scans. Imaging parameter were as follows: Section thickness 5mm, 1,5 mm gap, 96x128 matrix, 240mm FOV

- DWI: TE 100ms, b values 0 and 1000s/mm2,
- T2: "turbo gradient echo spin echo sequence"(TGSE), TR 7040ms, TE 115ms 160° flip angle,
- T1: spin echo, TR 560ms, TE 17ms, 70°flip angle.

Results and discussion

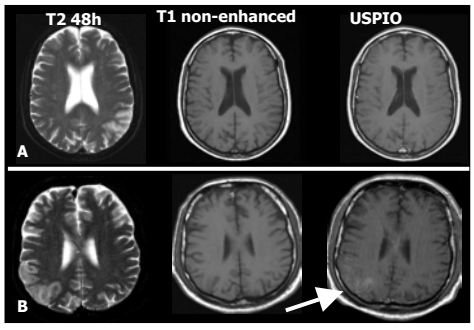
Infarct morphology

As a prerequisite of study inclusion, the initial scan showed territorial infarction Three patients were excluded from analysis due to withdrawal, hemorrhage transformation and protocol violation. The nine remaining patients showed infarcts of either supratentorial (n=11) or infratentorial (n=1) localization. Three 3 patients showed USPIO enhancement, whereas 6 patients did not. None of the patients studied showed Gadolinium enhancement. In the hemispheric infarctions, variable proportions of cortical and subcortical tissue damage were present. Whereas in the previous study all patients showed USPIO enhancement 5-7 days after ischemia onset(4), USPIO enhancement was a heterogeneous feature in strokes 3-4 days after stroke.



The distribution of USPIO enhancement within the infarcted tissue was heterogeneous. Fig. 2 shows an infarct of the whole MCA territory with USPIO restricted to subcortical areas (arrowhead). Supported by experimental data(2), pathogenetic concepts suggest that the striatum is more susceptible to ischemia, and ischemia development within the cortical areas may be postponed or avoided by collateral blood supply from pial vessels. Hence, the divergent USPIO enhancement may reflect differences in the pathogenesis and dynamics of infarct development in subareas of a given infarction.

Fig. 3 displays a pair of similar infarcts in two patients that were similar with respect to localization (posterior parietal cortex) and signal alterations. In both patients, cardiac embolism was the suspected cause of stroke. However, whereas the infarct in patient A did not show USPIO enhancement (right, upper row), the infarct in patient B showed a ribbon-like contrast enhancement in the outer zones of the infarct (right, lower row; arrow).



Conclusions

USPIO-enhanced MRI gives valuable new information after stroke. USPIO enhancement is not restricted to the subacute stroke but can be present in early stroke. USPIO enhancement is suggested to reflect divergent dynamics and spatial patterns of macrophage infiltration after stroke. Presence or absence of USPIO enhancement cannot be predicted by known clinical or MRI parameters. However, among the ten patients studied the following parameters did not separate infarcts with or without USPIO enhancement:

- localization: left/right; supra-/infratentorial; anterior, middle cerebral artery/ verebro-basilar territory,
- patient age,
- suggested embolic/non embolic etiology
- presence/absence of thrombolysis or tirofiban therapy

Hence, USPIO enhancement gives a truly new *in vivo* information in human stroke lestion. Early USPIO enhancement is suggested to reflect an early accumulation of macrophage in human cerebral infarcts. Therefore, USPIO enhanced MRI may help to select patients suitable for studying anti-inflammatory therapeutic strategies after stroke.

Acknowledment

Thanks to Guerbet for kindly providing Sinerem®.

References

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