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An alternative explanation of the origin of the signal in diffusion-weighted MRI

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Abstract I formulated an alternative explanation for the origin of the signal in diffusion-weighted MRI (DWI) and tested it in a simple experimental model using gelatin. My findings indicate that the signal in DWI is influenced by the passage of water from the sol to the gel state, independently of the presence of cell structures or membrane-dependent diffusion.

Key word Magnetic resonance imaging, diffusion weighted

Introduction

Diffusion is an expression of freedom of motion, and can be measured. In diffusion-weighted proton MRI (DWI) a radiofrequency pulse is applied which will saturate freely diffusing water, but spare water whose diffusion is limited, with the result that the latter will give higher signal. The currently dominant explanation for the signals observed in DWI involves the presence of a cellular medium and abnormalities of cross-membrane diffusion of water [1–3].

I formulated a hypothesis, based on reported clinical and experimental data, that the increased signal seen with restricted diffusion is related to the passage of water from the sol state (liquid water) to a gel state (gelled water), and set out to investigate this experimentally.

Materials and methods

A simple experimental model was used to test the hypothesis. I prepared some solid gelatin composed of about 98.4 % water, with 1.6 % protein and a trace of saccharide. This was placed in a glass cup, totally immersed in water. The test object thus formed was then placed within a standard head coil of an imager operating at 1.5 T, and imaged using a DWI sequence: repetition time 10,000 ms, echo time 92.6 ms, a 38 × 18 cm field of view, contiguous 5-mm-thick sections, 128 × 128 matrix, swapped frequency and phase, with saturation set for all three planes, and B values of 1 s/mm^2 (diffusion weighting virtually nil) and 1000 s/mm^2 (maximum diffusion weighting).

As a further test of the hypothesis, I imaged a subject with a normal brain, placing a small polystyrene cup containing gelatin alongside the head, and obtaining T2- and diffusion-weighted images, the latter with the maximum B value.

Results

When the sequence with a B of 1 s/mm^2 was used, the signal from the water in the cup was much lower than that from the gelatin, but when the maximum diffusion value (B 1000 s/mm^2) was applied, the situation was reversed (Fig. 1).

In the second experiment the signal from the gelatin in the cup was significantly higher than that from grey or white matter of the brain. The cerebrospinal fluid was normally saturated (Fig. 2).

Discussion

The most widely accepted explanation of the increased signal on DWI in a cerebral infarct invokes abnormal diffusion of water molecules across cell membranes

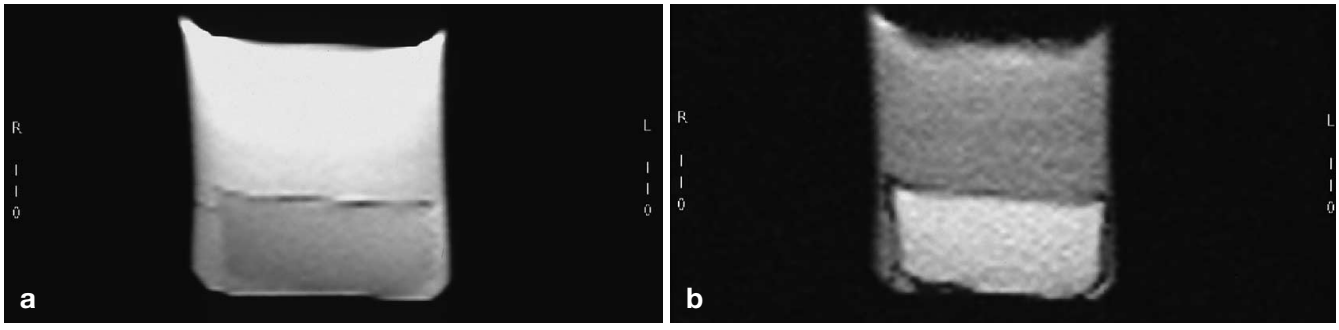

Fig. 1a,b Diffusion-weighted model, with gelatin immersed in water. **a** B = 1 s/mm^2: the signal from free water is higher than that from gelatin. **b** B = 1000 s/mm^2: the signal differential is reversed

[1–3]. However, it seems unlikely that MRI, which involves measurement of the radiofrequency signal from milimeter sized voxels, can demonstrate subtle differences in molecular motion. What clinical experience shows in practice is that DWI sequences are very sensitive to changes in the tissues in acute and subacute infarcts, but relatively insensitive to free cerebrospinal fluid, extracellular oedema without necrosis, neoplastic cells and most demyelinating lesions.

In ischaemic tissue the low ATP levels lead first to a defect in the sodium/potassium pump, with a consequent shift of water from the interstitial to the intracellular space. As homeostasis within the cell deteriorates, intracellular water may then combine with the proteins of the cytoplasm and enter a gel-like state. With prolonged ischaemia, autolysis begins, with the release from the cytoplasmic vesicles of catalytic enzymes which break down the organelles of the cell, reinforcing this process.

Gelatin is a good test substance, as it has a homogeneous, amorphous structure, which is insensitive to isotropic effects. Cell membranes or any equivalent structures are totally absent, so that one cannot explain signal changes on the basis of abnormalities of cross-membrane diffusion. The experiments indicate clearly that signal on DWI is influenced by whether the water in the substance being examined is in the sol or gel state. It is therefore reasonable to hypothesise that the signal obtained using the DWI sequence may be related to necrosis per se, independently of the mechanism, and not to the relative water content of the tissue.

Assuming this explanation to be correct, it can be predicted that changes will be apparent on DWI in other pathological situations, whenever there are conditions for water-to-protein binding resulting in a gel

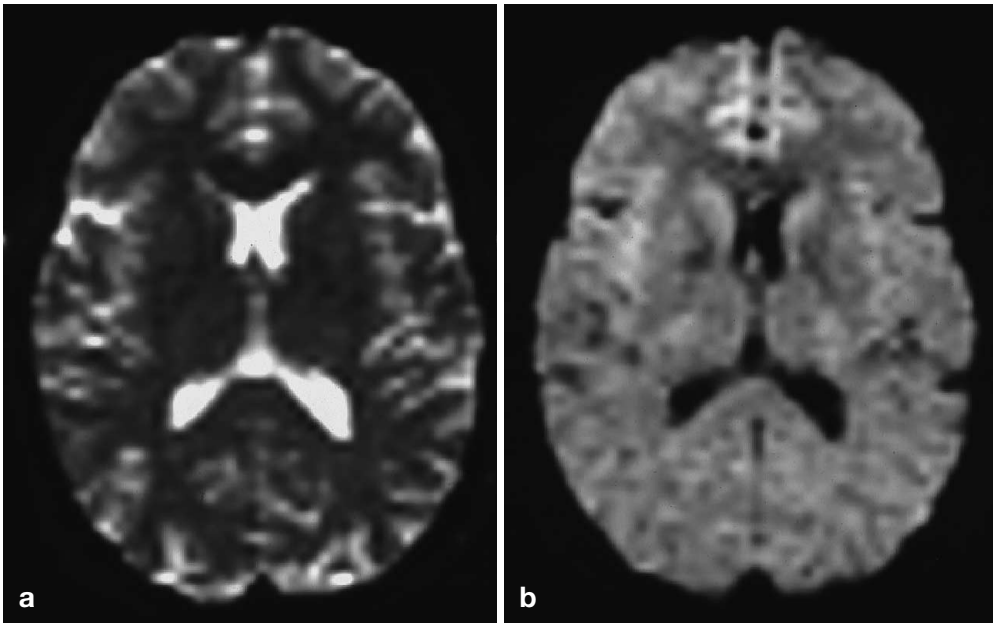

Fig. 2a,b Normal head with gelatin alongside it. **a** T2-weighted echo-planar image: both the cerebrospinal fluid (CSF) and the gelatin return high signal, while the signal from brain is intermediate. **b** Diffusion-weighted image, B = 1000 s/mm^2: the gelatin gives higher signal than the brain, while CSF gives low signal

medium. Examples are some cases of colloid cyst, abscesses or necrosis caused by direct trauma, necrosis occuring in tumours, or related to severe inflammation in multiple sclerosis. Some of these "false positives" have, indeed, been reported [4–8]. In other situations in which there is a shift of water from the extra- to the intracellular space, together with an impaired sodium/potassium pump, such as hypoglycaemia [9], there may also be evidence of restricted diffusion on DWI. It is also likely that a critically low temperature, restricting the free motion of water, will influence the diffusion signal.

From an analysis of the literature and the experiments reported here, I believe that the transition of water from a sol to a gel state is the single most important determinant of the signal in DWI.

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