

Persistent Cytotoxic Oedema after Ischaemic Stroke in the Context of the Glial-Neuron Unit: From a Magnetic Resonance Viewpoint*

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ABSTRACT

This article reviews the persistence of cytotoxic oedema after stroke as demonstrated by diffusion-weighted MRI and MR spectroscopy, and discusses the possible mechanisms of cooperative volume effects within the glial – neuron unit. The authors discuss the interpretation, diagnosis and, more importantly, characterisation of acute cerebral ischaemia.

Keywords: cytotoxic oedema, diffusion weighted imaging, MR spectroscopy, myo-inositol, stroke

INTRODUCTION

Diffusion weighted imaging (DWI) at present serves neuroradiologists in the characterisation of ischaemic lesions, which studies the restricted movements of proton spins in a condition referred to as cytotoxic oedema.¹ In particular, hyperintensities on images of high b-values or hypointensities on apparent diffusion coefficient (ADC) maps can last for days.² In this context, the pump leak model is generally quoted as the model that best explains the onset of cytotoxic oedema.³ However, it cannot explain why a restricted diffusion in the ischaemic tissue persists beyond the point in time of reperfusion by days.

A simplistic description of the multiple processes occurring during ischaemia, based on cell densities and shifts between the intracellular and extracellular spaces, is presented below as a pictorial essay. It is derived from the results of a previous study.⁴

BACKGROUND

By its nature, image contrast of DWI is averaged over different water environments and comprises both

diffusion and T2 sensitivity. This is due to the timing of the magnetic resonance (MR) pulse sequences. To establish diffusion sensitivity, a time segment of about 100 ms is generally used. During this time, averaging of different water environments, including membrane interactions, takes place.

Not only is the contrast in DWI multifactorial, but the cause of altered diffusion changes with time as well. The sequential order of events after stroke is perfusion deficit followed by an imbalance of the cerebral energy metabolism, cellular dysfunction and finally oedematous processes.⁵ The perfusion deficit triggers a cascade of biochemical reactions. The most harmful reactions are 1) membrane depolarisation leading to 2) Ca⁺⁺ penetration and glutamate release (this becomes a vicious circle), and 3) initiation of free-radical mechanisms. These various imbalanced homeostatic reactions are the cause of net volume shifts of extracellular into intracellular spaces, and thus of altered ADC values.

CONCEPT OF THE INTERPLAY BETWEEN ADC AND CELL DENSITY

The key behind this concept is the potential for ¹H MR spectroscopy to examine cellular densities and as such yields information that is complementary to ADC values. The creatine (Cre) level yields a good estimate

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of total cell density. This is because both neuronal and glial cells harbour Cre for their cellular homeostasis and energy needs. In addition, the Cre peak in the ^1H MR spectrum comprises both the phosphorylated and unphosphorylated form, regardless of huge variations in their relative compositions. As for fractional cell density, N-acetyl-aspartate (NAA) and myo-inositol (Ins) are ideal counterparts since NAA is located in the neuronal population and Ins in glial cells. However, during ischaemic events, these markers themselves become changed and are thus of limited use as markers of fractional cell densities.

We demonstrated recently that the Cre level correlates inversely with ADC after stroke.⁴ Immediately with the onset of stroke (all cells assumed to be vivid), the ADC falls to its lowest value, whilst Cre is at its normal (i.e. highest) level. Thereafter, ADC rises steadily as cells disintegrate and Cre begins to drop. We found a similar but weaker correlation between Ins and ADC.⁴ In addition, the ratio of Ins-to-Cre increases almost two fold between 15 h after stroke onset and 3.5 days later.⁴ This is interpreted as a temporary up-regulation of Ins as a non-harmful organic osmolyte, in line with reactive and swollen glial cells.⁶ This style signifies a breakdown of the close glial-neuron interaction.⁷ As far as NAA is concerned, a corresponding relationship with ADC was not found. There is little doubt that a low number of neurons results in a low NAA level, but the mechanism is less clear as to why NAA decreases significantly out of proportion to the progress of ischaemia.

We used short TE ^1H MR spectroscopy (STEAM with TR 3000/TE 20/NEX 128) for metabolic quantification and diffusion-weighted imaging (b 0, 500, 1000 s/mm²) to measure ADC values.⁴ In addition, each scan comprised FLAIR (T2) imaging, 3D time-of-flight MR angiography, and dynamic perfusion weighted imaging [bolus administration of 20 ml Gd-DTPA contrast agent]. For the latter, a series of 40 Echo Planar Image acquisitions per slice with a temporal resolution of 2s was collected after injection of the bolus. All studies were performed on a 1.5T scanner (Magnetom Vision; Siemens Erlangen; Germany).

PICTORIAL ESSAY

This shows a schematic diagram of a glial-neuron unit where cellular size and volume fractions change over time after stroke (Fig. 1).

Stroke onset shows an influx of Na^+ , Ca^{++} and water accompanied by a large increase of extracellular K^+

when energy requiring cell membrane transporters, namely the Na^+/K^+ -ATPase pump, begin to fail. Glial cells are known to be slightly more resistant to ischemia than neurons.⁸ *Characteristics: Usually the area of reduced ADC is smaller than the area of impaired perfusion (penumbra-core differentiation). T2-weighted images are negative.* This phase is normally missed in imaging observation as most stroke patients do not arrive at the hospital within this time frame.

Phase I depicts glial cells taking up K^+ in order to buffer the excess of K^+ released by the neurons. According to the principle of “ion control taking precedence over volume control”, neuron-glial interactions do not respond to homeostatic mechanisms by acting against osmosis.⁹ *Characteristics: Perfusion deficit* (Image 1b at time point of bolus passage in non-stroke affected tissue and thus hypointense, while the bright area reflects a delay between injection of the bolus and its arrival in the stroke lesion), *greatly lowered ADC* (in the core of the stroke lesion), *T₂ weighted images normal or slightly hyperintense, normal level of Cre and Ins, initial drop of NAA, strongly increased lactate.* Illustration case: Right MCA infarct at 6 hours after onset. The lesion-to-contralateral Cre is 0.9, the lesion-to-contralateral Ins is 1.1, and lesion-to-contralateral ADC is 0.34.

Phase II reflects glial cells becoming overwhelmed either by the number of K^+ ions or by the prolonged exposure time. Therefore, in time, the electrolyte is expelled from the glial cell to be replaced by Ins. Ins is up-regulated. *Characteristics: moderate T2 hyperintensity, lowered ADC, intermediate level of Cre, increased Ins to twice normal values, further drop of NAA, strongly increased lactate.* Illustration case: Right MCA infarct at 16.5 hours after onset. The lesion-to-contralateral Cre is 0.9, the lesion-to-contralateral Ins is 1.7, and lesion-to-contralateral ADC is 0.35.

Phase III portrays a late stage of cytotoxic oedema. Process of Ins down-regulation in activated glial cells. *Characteristics: pronounced hyperintensity, slightly lowered ADC, apparently normal Cre-to-Ins, yet further drop of NAA, increased lactate.* The increase in T2 originates from increased vascular permeability, which leads to pronounced vasogenic oedema. Illustration case: Left MCA infarct at 82 hours after onset showing the lesion-to-contralateral Cre is 0.7, the lesion-to-contralateral Ins is 0.7, and lesion-to-contralateral ADC is 0.46.

Phase IV reflects cell lysis and cell shrinkage (for example, neuronal loss which also results in an enlarged interstitial space). *Characteristics: T2 towards cystic infarction, elevated ADC, barely detectable levels of metabolites, remaining lactate.*

CONCLUSION

While it is generally understood that strokes are irreversible by the time T2 signal change occurs, it has not been well appreciated that the increase of Ins on ¹H MR spectroscopy also signifies the same. At this stage after stroke, the glial cells are overwhelmed by the ionic imbalance and the stroke is no longer reversible.

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