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Cerebro-vascular disease: morphologic imaging

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1. Introduction

The introduction of new functional magnetic resonance techniques, together with the technological progress in hardware (magnets, gradients, coils) and software (acquisition sequences and post processing), has improved the performance of magnetic resonance devices, and enabled extremely fast acquisition of functional-metabolic data on the brain. These techniques are perfusion and diffusion imaging, and are today, together with conventional sequences, considered vital for the pathophysiological and prognostic characterisation of central nervous system diseases. In particular, diffusion-weighted imaging (DWI) sequences have proved to behighly sensitive in the study of acute ischaemic pathology and in differentiating clinical pictures similar to stroke from other conditions with focal neurological deficits, including vascular, traumatic and inflammatory disease, and tumours.

2. Basic concepts and physical principles of diffusion

Diffusion involves the migration of molecules of water with random trajectories within biological structures and which collide against each other, because they undergo thermal molecular motion (Brownian motion). The distance (L) which a molecule can travel in a given fluid in time (T) is described by Fick's law, whereby the flow of molecules of the solute in a particular direction is directly proportional to the concentration gradient through a proportionality constant (D, diffusion coefficient in mm2/s) which depends in turn on the temperature and viscosity of the fluid and the molecular weight of the diffusing molecule. In the case of pure water D = 2.3*10-3mm2/s [1], and is 2-3 times less in the molecules of water of biological tissues [1, 2]. In the latter case, D is indicated by the term apparent diffusion coefficient (ADC) and is no longer calculated with Fick's law, but rather with a probabilistic method [3]:

$L = \sqrt{2D}\,T$

The reduction of D in biological tissues is explained by the presence of macromolecules, cellular and mitochondrial membranes, myelin sheaths and cytoplasmic organelles which tend to bond with a certain percentage of the water in tissue, diminishing its mobility and limiting its free diffusion. The diffusion of water molecules in biological tissue is therefore not only a function of temperature, but also depends on:

- permeability of the membrane;
- compartmentalisation of the water (extra-, intracellular);
- cell size;
- microscopic and ultrstructural characteristic of molecules

degree of anisotropy and orientation in space of the anisotropic fibres (the value of D is a function of the orientation of the fibres themselves). The phenomenon of diffusion was studied with MR for the first time in 1954 by Carr and Purcell [4], and its behaviour proved sensitive to a particular sequence proposed by Stejskal and Tanner [5] in 1965, which involves the application of two short-time high-intensity magnetic field gradients before and after the 180° pulse of a standard spin-echo sequence. The first gradient is capable of sensitising the protons of

the water molecules which acquire a precise phase difference on the basis of their position with respect to the gradient, whereas the second gradient acts on both the static water molecules and those which changed their position during the time interval between the application of the two gradients, giving them a net phase difference. This phase difference translates into a reduction of the phase coherence of the protons and therefore in a reduction of the magnitude of the echo which expresses a fall in the signal according to the relation [3]:

$$I=Io*e[-\gamma 2*G2*\delta 2*(\Delta-\delta/3)*ADC]$$

where:

ADC: apparent diffusion coefficient
I: intensity of the signal after the application of the gradients
Io: intensity of the signal before the application of the gradients
γ: gyromagnetic constant
G: width of the gradient
δ: duration of the gradient
Δ: time interval between the two gradients

The term $\gamma 2*G2*\delta\ 2*(\Delta-\delta/3)$ in the equation can be expressed with b, such that the equation becomes:

$$I=Io*e\ (-b*ADC)$$

The dependence of the factor b on the square of the intensity of the gradient is intuitive, due to the need for MR devices capable of producing single pulse high-intensity gradients and echo-planar sequences [6], to acquire images of the brain with a slice thickness of 6 mm, in less than a minute, in the three spatial planes.

3. Normal brain and diffusion imaging

The study of the brain structure can be performed on three different levels which correspond to different stages of processing performed by the software. These three levels are:

1. diffusion-weighted images;
2. ADC maps;
3. diffusion-tensor images.

The representation of diffusion-weighted images, with respect to the departure signal, will always depend on the loss of signal intensity which will be greater in correspondence with the greater value of D. Any sequence can be modified with the use of appropriate magnetic field gradients to obtain data relative to the movement of water molecules caused by their diffusion in the direction of the gradient itself. The data provided are only of a qualitative nature with respect to D, because the signal remains correlated to dependence on T1, T2 and the proton density of the base sequence.

The diffusion coefficient of protons in the cerebrospinal fluid is very high, similar to that of pure water. This determines a loss of signal and therefore a hypointensity of the cerebrospinal liquor-containing spaces with respect to the brain parenchyma (figure 1) [2, 3]. The loss of signal in the grey matter (e.g. in the basal gonglia), where D is nearly three times lower than in the ventricles, is much lower than in cerebrospinal fluid [2]. Whereas both in cerebrospinal fluid and in grey matter water diffuses isotropically regardless of the direction in which the gradient

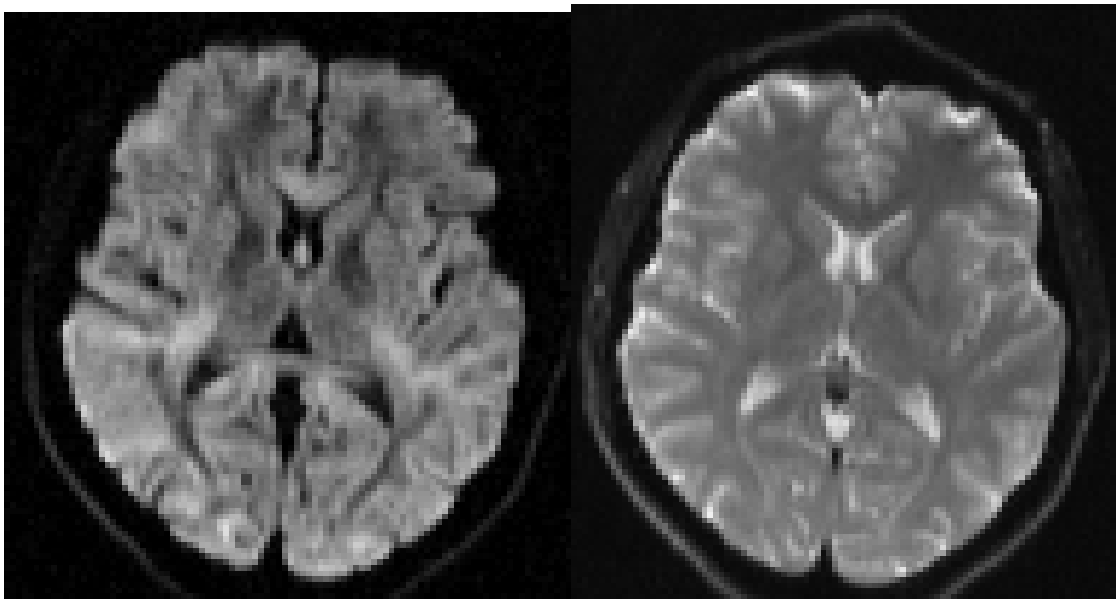

Figure 1. Normal brain tissue in DWI images without (left) and with gradient application. Note that cerebro-spinal fluid shows lower signal than brain parenchyma on DWI images with gradient application.

is applied, and the signal will have the same intensity, the situation is much more complex in the white matter. In fact, normal grey matter, with an organised and compact cellular structure, diminishes the movement of water molecules, and demonstrates no directional obstacle to diffusion. These characteristics are known as isotropy. The distribution of the axonal fibres, according to the orientation of the diffusion gradients, modifies the ADC values. The white matter oriented in the direction of the diffusion gradients has high levels of ADC, whereas the white matter oriented transversely with respect to the diffusion gradients have much lower ADC values (anisotropy).

The ADC of grey matter is lower than that of white matter arranged parallel to the direction of the diffusion gradients, whereas it is greater than that of white matter arranged transversely.

Because the structures with low ADC values appear hyperintense in diffusion-weighted images, the fibres of white matter positioned transversely to the direction of the diffusion gradient in the craniocaudal axis, such as the middle cerebellar peduncle, the splenium of the corpus callosum and the superior longitudinal fascicle, are hyperintense with respect to the grey matter in diffusion-weighted images.

The white matter fibres arranged parallel to the direction of the diffusion gradients include the internal capsule and the corona radiata which are strongly hypointense. The remaining portions of cerebral white matter are slightly hypointense with respect to the grey matter. Anisotropy can create diagnostic problems. For this reason modern devices are able to provide images known as isotropic, in which the gradients are sensitised to diffusion in the three directions in space. This eliminates the effects of anisotropy [8].

Through the acquisition of at least two, differently sensitised, images, ADC maps enable diffusion-weighted sequences to be rendered independent from T1 and T2 relaxation times. The image calculated in this way will reflect the value of the ADC in every voxel. It should be noted

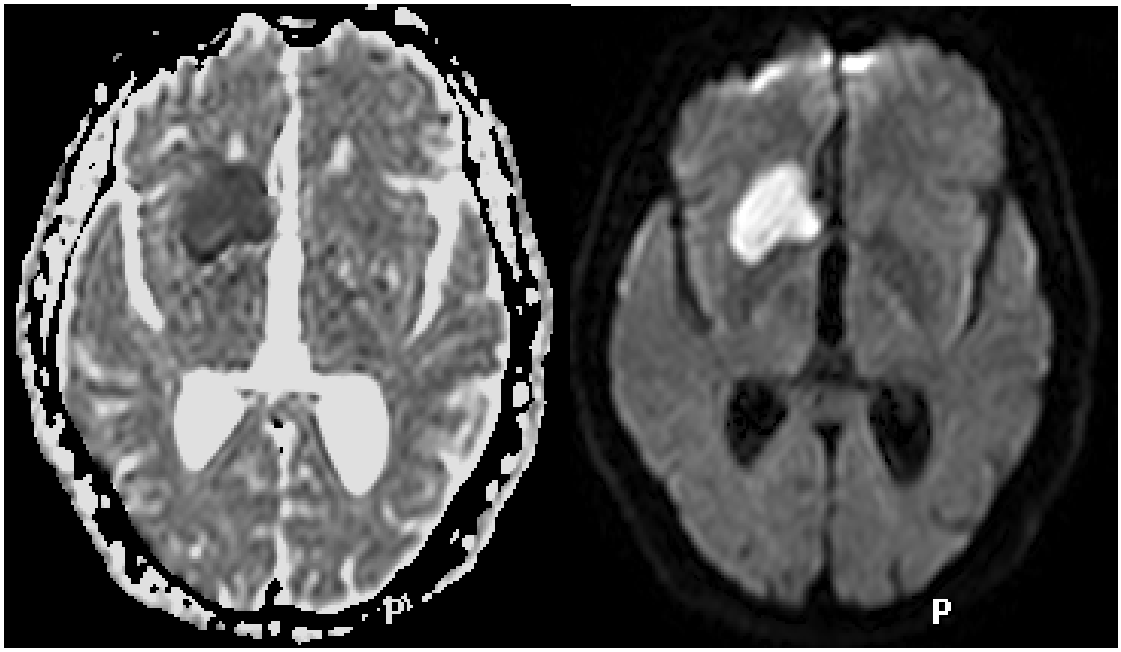

Figure 2. Ischemic lesion in DWI (left) and ADC map.

that the contrast in ADC maps, which provides a direct value of the D value, is completely opposite to that of the diffusion- weighted image. The advantage of rendering the image independent of the influence of T1, T2 and proton density facilitates the interpretation of those pathological areas which present similar signal intensities in the standard sequences, since these sequences are unable to associate them to a real variation in diffusion. The maps obtained with diffusion tensor imaging, for which a mathematical description is available in the literature [9-11], render the diffusion-weighted images independent of the orientation of the gradients with respect to the position assumed by the structures being studied, enabling the study of non isotropic structures whose spatial orientation is unknown before the performance of the MR examination. In this way a system of coordinates characterised solely by the diffusive property of the water of the tissue can be created for every voxel, regardless of the orientation of the patient within the magnet. To calculate the tensor at least six diffusion-weighted images with gradients oriented in different directions need to be acquired, as well as an image not dependent on diffusion.

4. Clinical applications in Cerebral ischaemia

The main application of DWI is in the assessment of hyperacute ischaemic lesions [12-15]. Within minutes of the ischaemic event a significant reduction in the diffusion of water molecules in the damaged brain tissue takes place [16-19]. The biochemical basis for this process is not completely understood, although an important contribution is provided by the cytotoxic oedema associated with limiting diffusion [20]. The most likely explanation suggests a reduction in blood flow in that phase and as a consequence a reduction in the energy substrates necessary for cerebral metabolism. This would lead to an adenosine triphosphate (ATP) depletion; damage to the Na+-K+-ATP pump and other ionic pumps incapable of maintaining

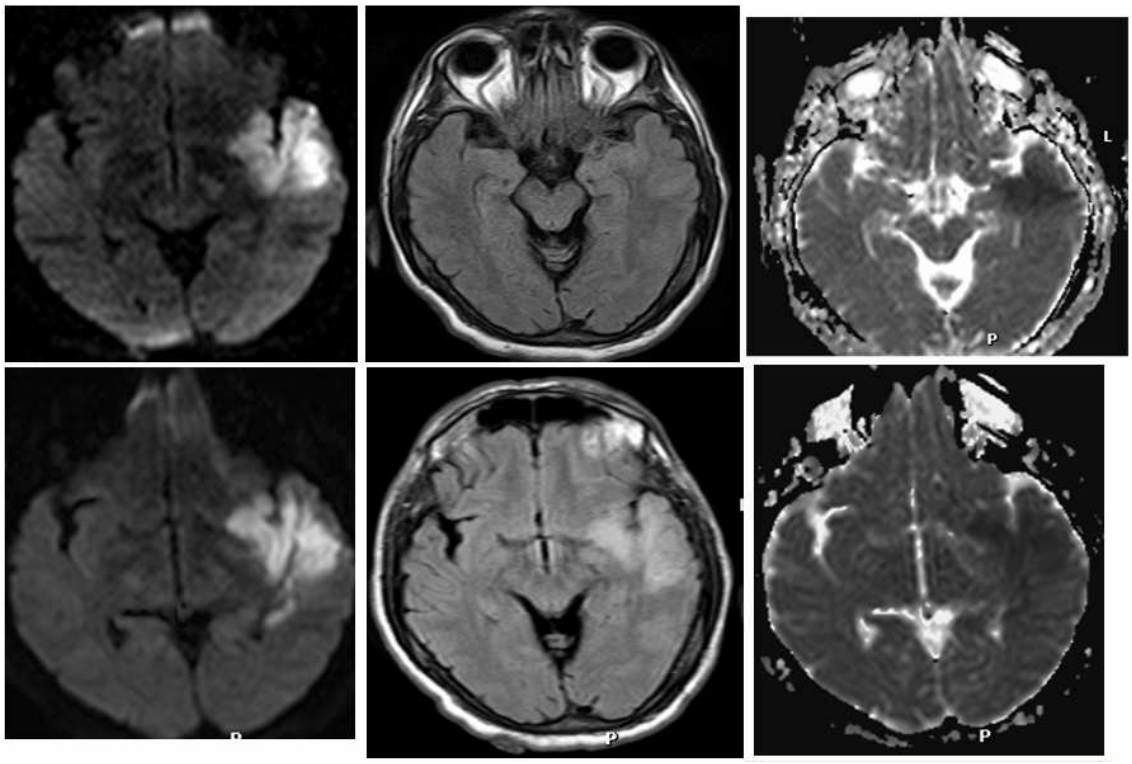

Figure 3. Ischemic lesion changes over time. Acute (up) and subacute (down). In the acute phase no signal changes are evident in T2 FLAIR (middle) which become positive some days later. ADC signal decrease over time.

intracellular homeostasis, a flow of Ca++ and Cl- ions from the extracellular to the intracellular space, and, following the loss of ionic gradients, a recall of water molecules from the extracellular compartment which accumulate within the cell increasing its size (cytotoxic oedema). Other causes are the reduction of extracellular space, and the increase in viscosity, temperature and permeability of the membrane [21-24].

This situation leads to a decreased diffusion capacity of the water molecules in the intra-cellular space, a condition which is visualised in diffusion-weighted images as a focally hyperintense signal in the ischaemic area with respect to the healthy parenchyma (figure 2). The value of ADC corresponding to the hyperintense area appears decreased, determining a hypointense signal in the related maps. This decrease in ADC values is at a peak 8-32 hrs after the acute event, and remains noticeably decreased in the following 3-5 days to then return to normal 1-4 weeks following stroke onset [24-27]. This pattern can vary in the case of early reperfusion, with «pseudonormalisation» of ADC values as early as 1-2 days after stroke onset (figure 3).

The persistence of the decreased values of ADC reflects the persistence of the cytotoxic oedema, associated with a restriction of diffusion, followed by the development of vasogenic oedema and the destruction of cell membranes, with the consequent increase of the extracellular water and therefore of diffusion.

The assessment of the ADC values has a predictive role regarding the evolution and severity of the ischaemic damage [28], which is particularly important in the hyperacute phase when the ischaemic focus is characterised by a central core, with markedly decreased ADC

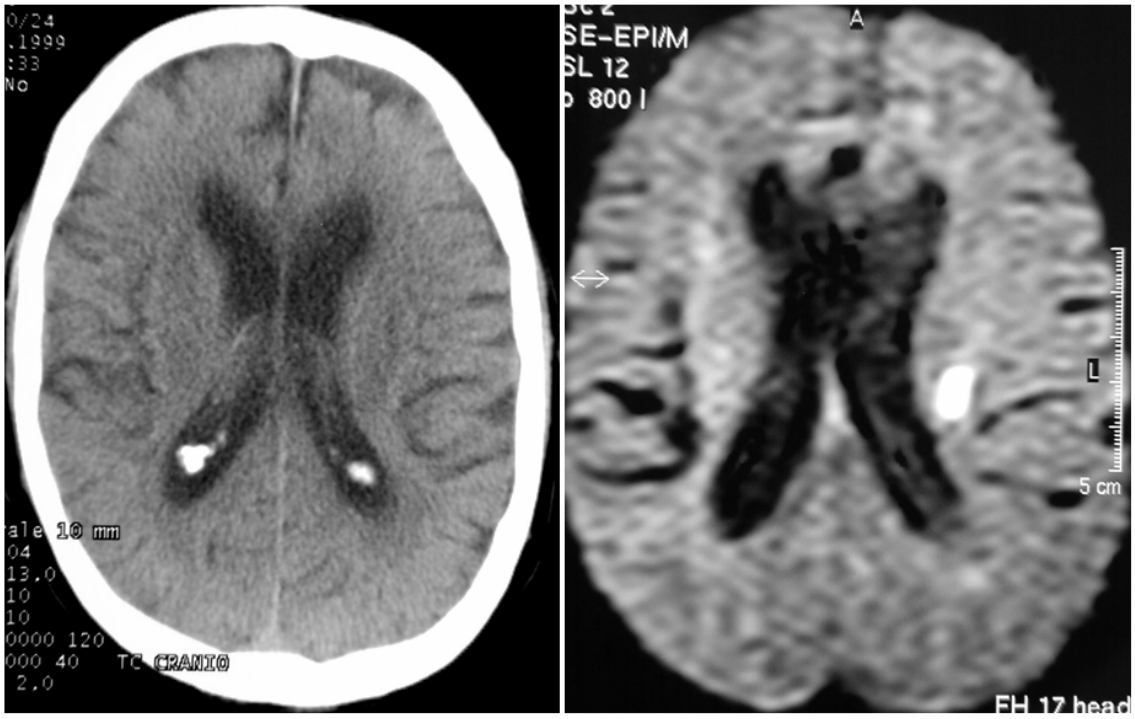

Figure 4. DWI (right) is more sensitive than CT (left) in detecting the ischemic lesion.

values, and by a larger peripheral portion where the phenomenon is less marked (area of ischaemic penumbra or area at risk of infarct). In this phase the combination of diffusion imaging and the perfusion examination which studies microvascular haemodynamics is particularly important.

Using principally the blood volume value (rCBV), the combined assessment of diffusion and perfusion parameters is capable of identifying three possible patterns [27, 29-32]:

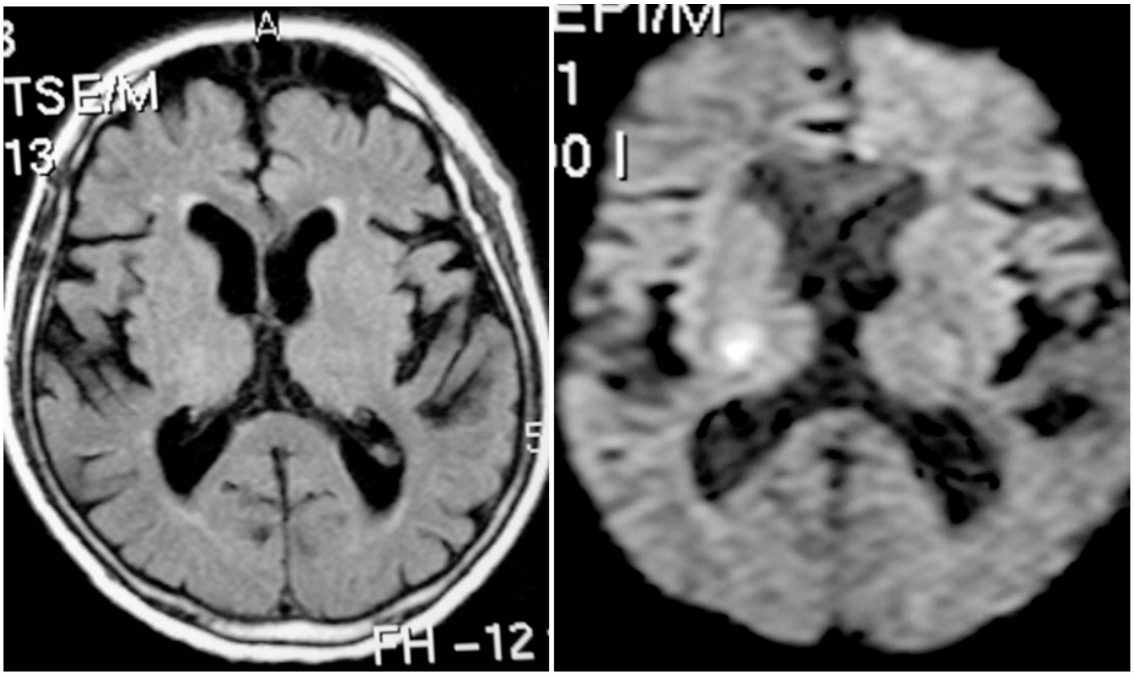

Figure 5. DWI (right) is more sensitive than T2 FLAIR.

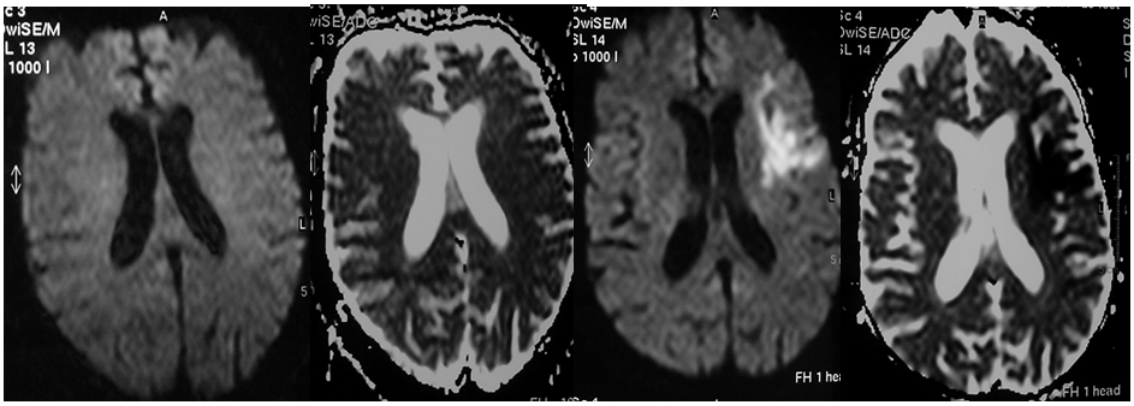

Figure 6. Hyperacute ischemia (left) might be normal on DWI.

- lesions smaller in diffusion than in perfusion (55-77%
- of cases) (figure 8);
- lesions of the same size or, more rarely, larger
- in diffusion than in perfusion;
- lesions observed in diffusion but not in perfusion.

The first pattern, which is more frequent and seen particularly in ischaemic lesions which involve larger diameter vessels (for example in the proximal middle cerebral artery), indicates the presence of a tissue at risk in the ischaemic penumbra which has not yet suffered infarction but is hypoperfused and therefore susceptible to fibrinolytic treatment with the possibility of the restoration of normal blood flow. In non-treated patients in general, the alteration observed in diffusion tends to increase in time, reaching a size similar to that of the alteration in perfusion. Flow (rCBF) and transit time (MTT) parameters, on the other hand, on average tend to overestimate the size of the infracted area.

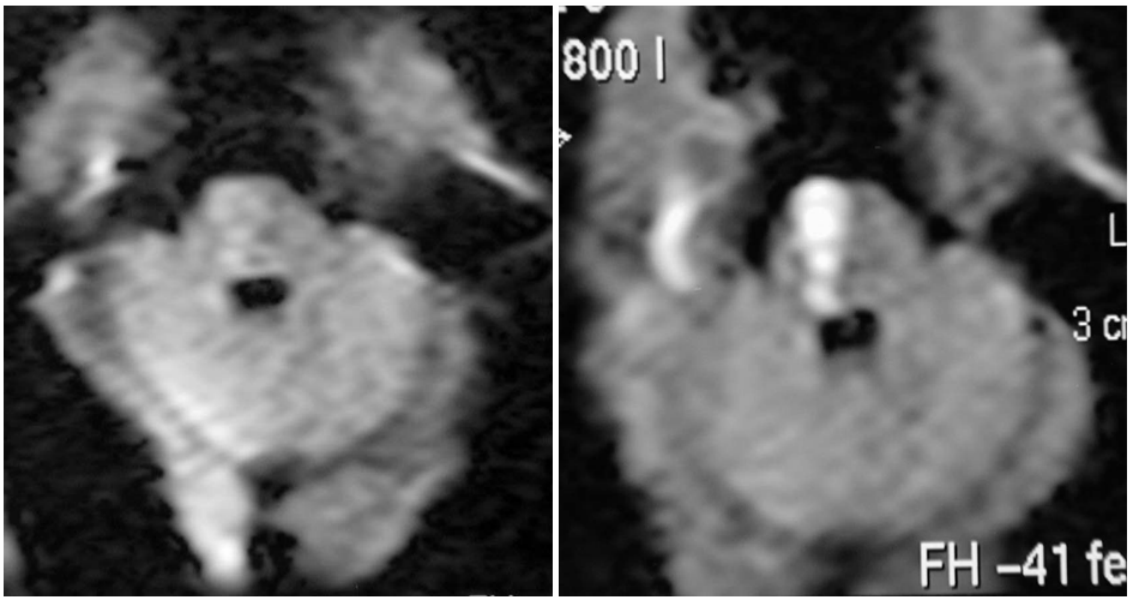

Figure 7. Hyperacute infratentorial ischemia (left) might be normal on DWI

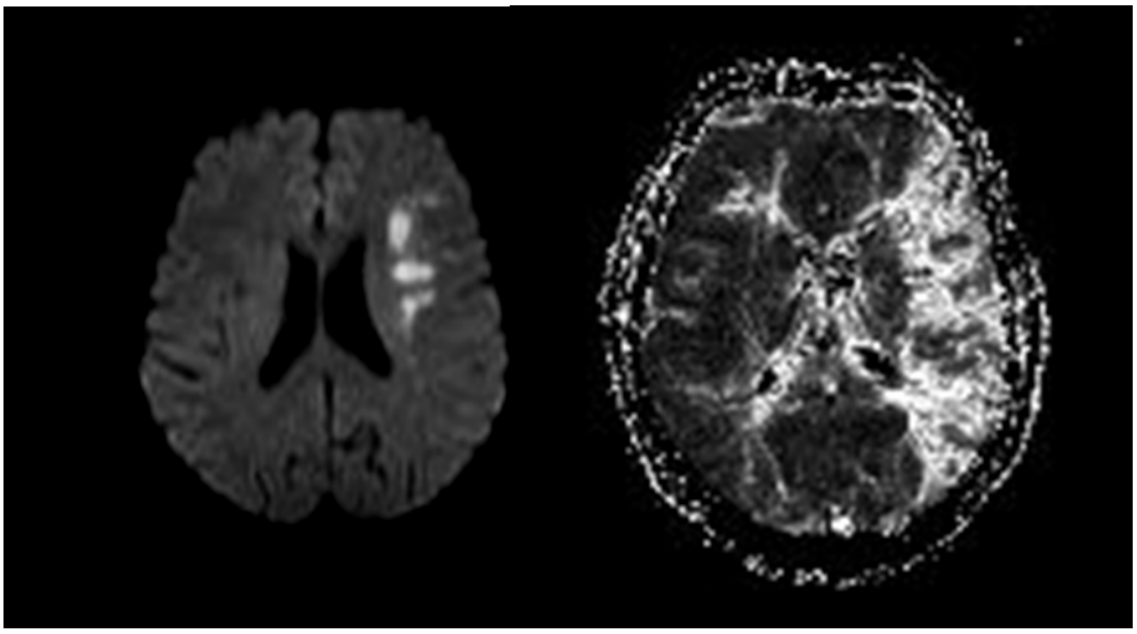

Figure 8. Perfusion MRI deficit (right) can be more diffuse than DWI alteration (left). The so called perfusion/diffusion mismatch.

In the case where the perfusion deficits are smaller than those in diffusion or absent (when the vessels involved are smaller in size as with infarcts of the perforating arteries and of the most distal portion of the middle artery), or in the case of reperfusion of the infarcted area, therapies involving neuroprotectors prove more appropriate [33, 34]. DWI images are more sensitive than CT (figure 4) and conventional MRI (figure 5).

False negatives in diffusion have been reported in the case of small-sized infarcts of the posterior cranial fossa, and/or infarcts studied at a too early stage (Fig. 6, 7). Wang [35] analysed the causes that may determine this event, identifying three possible mechanisms. The cerebral flow could be at an intermediate level with respect to the neuronal damage threshold, but nonetheless above the threshold of decreased diffusion. The reduction in neuronal electrical activity occurs when cerebral perfusion is between 15 and 20 mL/100 g per minute even though the membrane pump damage (which is due to diffusion alterations of water molecules) does not occur until celebral blood flow reaches 10-15 mL/100 g per minute. A second mechanism may be due to reperfusion, which would return the cerebral tissue to a normal situation before cytotoxic oedema sets in.

Thirdly, there is the possibility of a second ischaemic event having occurred after the negative diagnosis obtained with diffusion. It should be remembered that negativity in diffusion can be accompanied by positivity in the perfusion maps.Therefore, integrating the two techniques is a good strategy for coming as close as possible to a correct diagnosis.

False positives in diffusion sequences can also occur in patients with stroke symptoms but with a non-ischaemic diagnosis [36, 37].

It should be noted that there is the possibility of anomalies in DWI in the first hours after the onset of symptoms which do not appear in later examinations [38]. This is due to lesions known as reversible ischaemias. Karonen [38] demonstrated that this situation occurs in only

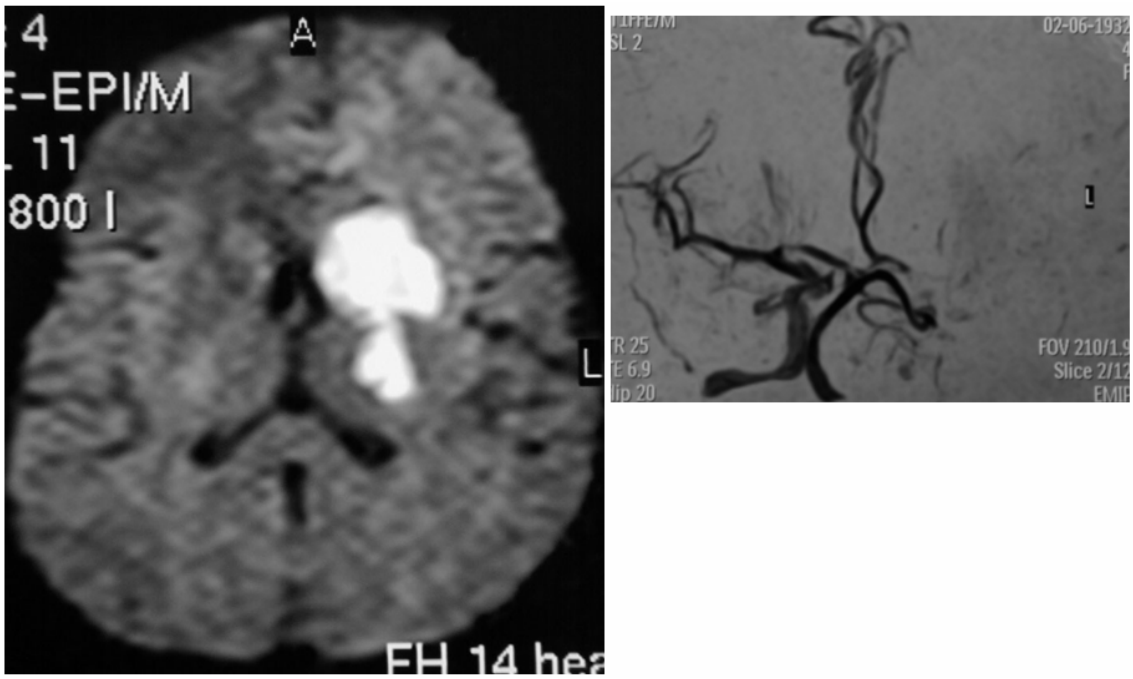

Figure 10. FMR angiography (right) can show the arterial occlusion in a patient with acute ischemia and DWI alteration.

about 2% of patients with lesions in DWI. However, the situation is different with regard to patients undergoing venous or arterial fibrinolytic treatment in whom the reduction or reversibility of the DWI alterations is more common (figure 5) [39-41]. The reversibility of lesions observed in diffusion has been demonstrated in laboratory animals, but few studies have examined the issue in humans. Hasegawa et al [42] found that a critical intensity threshold exists for these reversible alterations, which are quantifiable with ADC maps. The ADC maps, therefore, may be able to discriminate tissue which could be saved from the ischaemic event. This concept, however, was not supported by Minematsu et al [43], who nonetheless showed that reversible lesions are in general less hyperintense in DWI than irreversible lesions.

In patients with transient ischaemic attack (TIA) the positivity of diffusion imaging is close to 50% (figure 6) [44, 45]. This percentage increases proportionally to the total duration of the symptoms and is characterised by lesions with decreased diffusion. If the patients are divided into groups on the basis of the TIA duration, the rate of DWI-positive cases oscillates between 0% and 67%, and is greater the longer the duration of the ischaemic event. Of the patients with TIA lasting up to 1 hr, only 33% have lesions visible in DWI, whereas in patients with TIA between 12 and 24 hrs the figure increases to 71% [46]. In one study 20% of lesions in patients with TIA were no longer visible in the follow-up examination [44]. DWI can also be useful in documenting the presence of acute or subacute lesions in the context of previous multi-infarct damage. This can be useful from the prognostic and diagnostic point of view.

The use of diffusion sequences has also been proposed for the study of leukoaraiosis. Leukoaraiosis [47] is a radiological finding of unknown pathogenesis characterised by the presence of circumscribed or diffuse areas of white matter which appear hypodense in computed tomography (CT) and hyperintense in MR sequences with long repetition times [48, 49]. The

presence of this finding is thought to be due to a process of chronic cerebral ischaemia localised mainly in the periventricular white matter and the white matter of the semi-oval centre. Leukoaraiosis is characterised by axonal loss and proliferation of glial cells [48]. The axonal loss contributes to an increase in ADC, because the axons determine a significant «impediment» to the diffusion of water. The axonal loss leads to an increase in the content of free water in the tissue. This then determines a reduction in «fractional» anisotropy in the regions of leukoaraiosis and an increase in the values of ADC.

MR angiography is currently used to show the brain vasculature in the acute phase of brain ischemia being able to show eventual vessel occlusion (figure 10) which may be treated with intravenous or intra-arterial approach.

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