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Review Article

Applications of diffusion-weighted and diffusion tensor MRI to white matter diseases – a review

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ABSTRACT: This paper reviews the current applications of diffusion-weighted and diffusion tensor MRI in diseases of the brain white matter. The contribution that diffusion-weighted imaging has made to our understanding of white matter diseases is critically appraised. The quantitative nature of diffusion MRI is one of its major attractions; however, this is offset by the more advanced hardware required to collect diffusion-weighted images reliably, and the more complex processing to produce quantitative parametric diffusion images. With the now common availability of scanners equipped to perform echo-planar imaging, the acquisition of diffusion tensor images is sure to become more widespread and routine. Copyright © 2002 John Wiley & Sons, Ltd.

KEYWORDS: diffusion; tensor; MRI; DTI; white matter; disease

INTRODUCTION

The molecular translational motion of tissue water forms the basis of clinical diffusion-weighted (DW) magnetic resonance imaging (MRI).[1] In biological tissues, diffusion may be hindered by interactions with barriers such as cell membranes and organelles.[2] Instead of spreading out with a Gaussian distribution, diffusing molecules may be reflected by, or at least have their mobility interrupted by, interactions with the cell membranes and other intracellular and extracellular structures. Thus, the shape of the distribution of a parcel of diffusing molecules is influenced by these interactions, and in some sense will conform to the shape of the compartment that is accessible to the diffusing molecules. Of course, with MRI, we do not measure the signal from just a few of the spins, but the total signal from all spins within an image voxel. Thus we are measuring the volume-averaged propagation of the diffusing molecules as they interact with the cellular structures present with the voxel.

Because the water molecules are no longer able to move freely, diffusion in biological systems is termed hindered diffusion. The diffusion coefficient that is measured in a large sample of fluid characterizes the rate at which a parcel of fluid at a given location subsequently spreads out. This is termed the 'bulk' diffusion coefficient, and depends on the chemical properties of the fluid and temperature of the sample. In biological tissues, the underlying physical properties of the tissue water are the same as in a bulk sample; however, the mean square displacement per unit time is lessened by the restricting barriers. Diffusion-weighted MRI provides a means of measuring these distances, and in biological systems it appears that the diffusion coefficient is lower than that of the bulk sample. Hence, the term apparent diffusion coefficient (ADC) was coined[3] in order to indicate that it is understood that the diffusion process is the same as in free water, but the mean square displacement per unit time is lessened by these interactions, not by a reduction in the diffusion coefficient.

Thus, it would seem that diffusion-weighted imaging might provide some insight into the nature and degree of pathological damage that occurs in diseases of the central nervous system (CNS) when cellular structures are

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Abbreviations used: AD, Alzheimer's disease; ADC, apparent diffusion coefficient; ALD, adrenoleukodystrophy; ALS, amyotrophic lateral sclerosis; CADASIL, cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy; CJD, Creutzfeldt–Jakob disease; CNS, central nervous system; CT, computerised tomography; DTI, diffusion tensor imaging; DW, diffusion-weighted; EPI, echo planar imaging; HIV, human immunodeficiency virus; MMSE, mini-mental state examination; MR, magnetic resonance; MRI, magnetic resonance imaging; MS, multiple sclerosis; MTR, magnetisation transfer ratio; NAWM, normal-appearing white matter; PP, primary progressive; RR, relapsing-remitting; SP, secondary progressive; WM, white matter.

damaged or disrupted as part of the pathological process. Furthermore, when the cellular structures are highly ordered, such as in the axonal 'fibres' within the white matter, diffusion tensor imaging would appear to offer something unique within MRI, because the directional nature of the diffusion-sensitizing gradients can encode properties that vary with direction. This paper reviews the applications and results of diffusion-weighted MRI and diffusion tensor MRI in disorders of the CNS, with emphasis on diseases mainly affecting the white matter.

MULTIPLE SCLEROSIS

Multiple sclerosis (MS) is an inflammatory autoimmune disease thought mainly to affect the white matter. The disease typically strikes in the third and fourth decades of life, and the disease course varies greatly from patient to patient. After presentation with transient acute symptoms, such as optic neuritis or numbness and pain in the limbs, there are usually periods of remission interspersed with acute attacks that have been linked with inflammatory events in the CNS. After this early relapsing–remitting (RR) disease course, a period of stability with few acute attacks may last for many years. The disease may then enter either the secondary progressive (SP) phase, with severe disability accumulating after the acute attacks, or the frequency of acute events may stabilize or even reduce, with little residual disability: this is the benign disease course.

The first report of the use of diffusion-weighted MRI in MS was in 1993, when Larsson *et al.*[4] showed an elevated diffusion coefficient in T_2-visible lesions. There are now several published studies of MRI diffusion measurements in MS; the emerging evidence from these is summarized below.

Elevated diffusivity in lesions

All studies[6–10] have shown, perhaps not surprisingly, that the mean diffusivity is elevated in lesions seen on T_2-weighted scans. The degree of elevation seems to depend somewhat on the clinical course of the patient, but can be as high as 250%, with some lesions having diffusivity close to that of pure water at body temperature.

Attempts have been made to discriminate between lesions in different clinical sub-groups of MS. First, patients with a benign disease course were compared with those with an SP course, but no differences in diffusivity were seen.[5] More recently, relapsing-remitting disease was compared to SP, with more striking differences between lesion diffusion characteristics. In one study,[11] the mean diffusivity was about 50% higher in SP lesions compared to RR lesions, while in another[12] there was a significant increase in average diffusivity in SP patients, as measured from whole-brain diffusivity histograms.

Table 1. Reported increases in diffusivity in MS patients' normal-appearing white matter compared with healthy control subjects' white matter

Literature source	Increase in diffusivity
Christansen *et al.*[5]	8.5%
Horsfield *et al.*[6]	12.7%
Werring *et al.*[8]	4.8%
Bammer *et al.*[9]	3.5%
Filippi *et al.*[14]	12.9%

No post-mortem correlations with pathology have been performed for diffusion parameters. However, a number of groups have compared mean diffusivity with other MR imaging techniques that are thought to correlate with move severe axonal damage. These include lesions that are hypointense on T_1-weighted scans (black holes) and lesions with low magnetisation transfer ratio (MTR) values: those lesions with more destructive pathology are generally shown to have the most strongly elevated diffusivity.[6–10,13]

Elevated diffusivity in normal-appearing white matter

A pattern of slightly elevated diffusivity, evident from even the earliest work, strongly suggests that there are abnormalities in the so-called normal-appearing white matter (NAWM) between the T_2-visible lesions. The elevation in diffusivity of around 4–8% (Table 1) in NAWM suggests that either MS is a diffuse WM disease as well as multi-focal in nature, or the WM is subject to Wallerian degeneration proximal and distal to the visible lesions.

Reduced diffusion anisotropy

Reduced diffusion anisotropy could result from either of two causes: damage to and removal of highly-aligned cellular structures such as axons; or replacement of axonal fibres with more amorphous cells such as glial cells. Two recent studies show that diffusion anisotropy is generally reduced in MS lesions.[8,9] However, one study showed the lowest anisotropy in acute inflammatory lesions,[8] while the other showed that T_1-hypointense lesions (black holes) have the lowest anisotropy.[9]

Figure 1 shows T_1-weighted, T_2-weighted and diffusion tensor images obtained by Werring *et al.*[8] in an MS patient (reproduced with permission), in which a ring-enhancing lesion is clearly evident on T_2-weighted and post-contrast T_1-weighted images [Fig. 1(a) and (b)]. The fractional anisotropy image [Fig. 1(c)] exquisitely

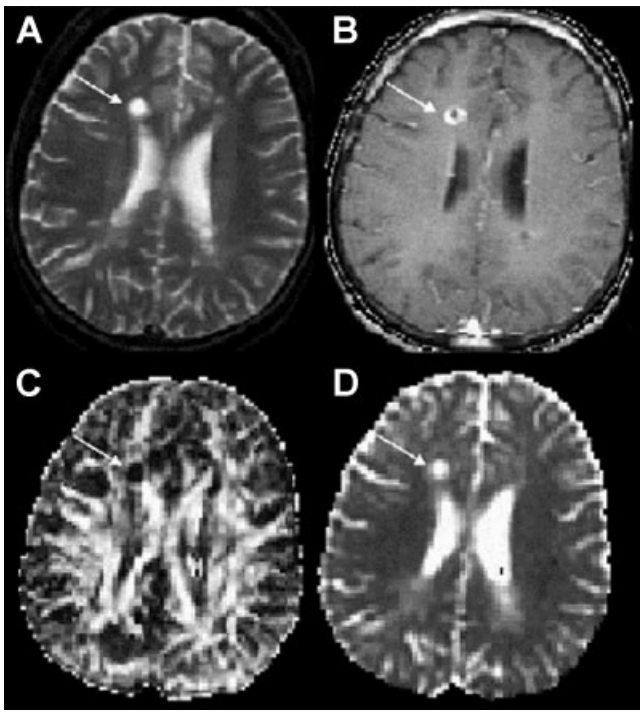

Figure 1. MR appearances of an MS lesion in axial section (reproduced with permission from Werring *et al.*[8]). (A) T_2-weighted image in which the lesion appears hyperintense. (B) Post-contrast T_1-weighted scan in which a rim of hyperintensity surrounds the core of the lesion. (C) Fractional anisotropy image, in which the intensity of the image is directly proportional to the anisotropy. Note the marked loss of structure/anisotropy within the lesion. (D) Mean diffusivity image (trace/3). The lesion exhibits high signal intensity suggesting little hindrance to diffusion due to breakdown of tissue structure

demonstrates loss of tissue structure within the lesion, which in turn has led to a reduction in hindrance to diffusion and therefore high apparent diffusivity [Fig. 1(d)].

Assessment of anisotropy is clouded by the fact that anisotropy varies throughout the white matter,[15] and so, in order to make fair comparisons, a reference value of anisotropy is really required against which changes can be compared. The exact location of a lesion, even to within a few millimetres, can have a large influence on the measured anisotropy in normal subjects.

Sensitivity to inflammation

The formation of a new MS lesion, or the reactivation of a pre-existing lesion, is thought to be accompanied by opening of the blood–brain barrier; this shows on a T_1-weighted image with intravenous contrast agent as a hyperintense area. Two recent studies[16,17] have shown that there appears to be subtle changes to the NAWM that precede visible enhancement with Gd-DTPA contrast agent. This exciting finding points to the possibility that blood–brain barrier breakdown may not, as was previously thought, be the primary event in a cascade leading to demyelination and possible permanent tissue damage. Intriguingly, Werring *et al.*[17] also showed subtle changes in diffusivity in the contralateral hemisphere, thought to be caused by injury to the axons that cross the mid-line after passing through the visible lesion.

ISCHAEMIC LEUKOARAIOSIS

Leukoaraiosis (*leuko* meaning 'white' and *araiosis* meaning 'rarefaction') is the non-specific name given by Hachinski *et al.*[18] to describe the radiological appearance of diffuse changes in the periventricular white matter seen either on CT or MR images. The clinical symptoms are variable but may include subcortical dementia, lacunar stroke, problems with gait and Parkinsonian features. Leukoariotic appearances may be observed in a range of disease states including chronic ischaemia, CADASIL and Alzheimer's disease (see below).

Jones *et al.*[19] applied DT-MRI to a study of nine patients with ischaemic leukoaraiosis and 10 age-matched controls. They defined ischaemic leukoraraiosis as the radiological appearance of diffuse periventricular white matter changes on conventional MR imaging in patients with a history of lacunar stroke and/or a subcortical dementia believed to be of vascular origin.

In regions of T_2-weighted hyperintensity, a characteristic pattern of elevated mean diffusivity and reduced anisotropy was observed (Fig. 2). For example, in right frontal subcortical white matter the mean diffusivity was elevated ($1.12 \pm 0.15 \times 10^{-3}$ mm^2 s^{-1}) in leukoaraiotic subjects compared to controls ($0.75 \pm 0.11 \times 10^{-3}$ mm^2 s^{-1}), while fractional anisotropy was reduced in leukoaraiotic subjects (0.53 ± 0.11) compared with controls (0.78 ± 0.09). These results are highly consistent with histopathological findings of axonal loss and proliferation of glial cells in leukoaraiosis.[20,21] The mean diffusivity observed in leukoaraiosis is significantly lower than that observed in necrotic tissue such as found in a lacunar infarct. Jones *et al.*[19] attributed this to proliferation of glial tissue (observed in post-mortem histological examinations), which serves to hinder the diffusion of water molecules.

Interestingly, a strong negative correlation was found between mean diffusivity and fractional anisotropy in regions of T_2-weighted hyperintensities ($r = -0.92$; $p < 0.0001$), as reproduced in Fig. 3. The figure also includes data obtained from within the core of necrotic infarcts, secondary to carotid stenosis, obtained in three additional subjects, which serves to illustrate the difference in diffusivity between necrotic tissue and leukoaraiotic tissue. It was suggested by Jones *et al.* that the difference in mean diffusivity observed for the same low diffusion anisotropy in these two tissue types is

Q1

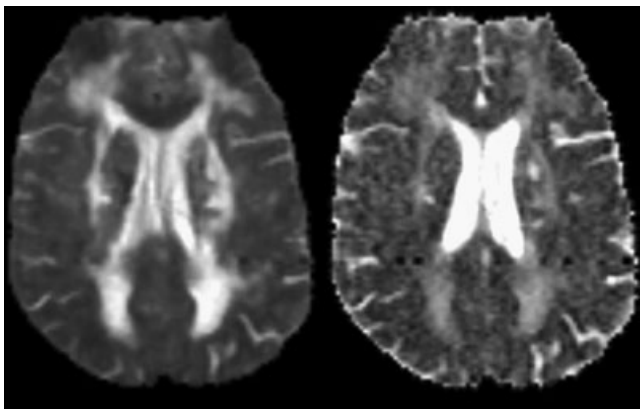

Figure 2. T_2-weighted and mean diffusivity images in a subject with leukoraraiosis (reproduced with permission from Jones *et al.*[19]). Left: T_2-weighted axial image. Note the regions of high signal intensity in periventricular regions confluent with the horns of the lateral ventricles. The signal intensity is comparable to that within the ventricles. Right: mean diffusivity image. Note that there is now a clear distinction between the lateral ventricles and the periventricular hyperintensities seen on the T_2-weighted image. The diffusivity is lower in the regions of leukoaraiosis compared with the 'free' water in the CSF-filled ventricles, which was attributed to proliferation of glial tissue in leukoaraiosis, which would hinder diffusing water molecules. Note also the punctate regions of hyperintensity, most likely reflecting lacunar infarction

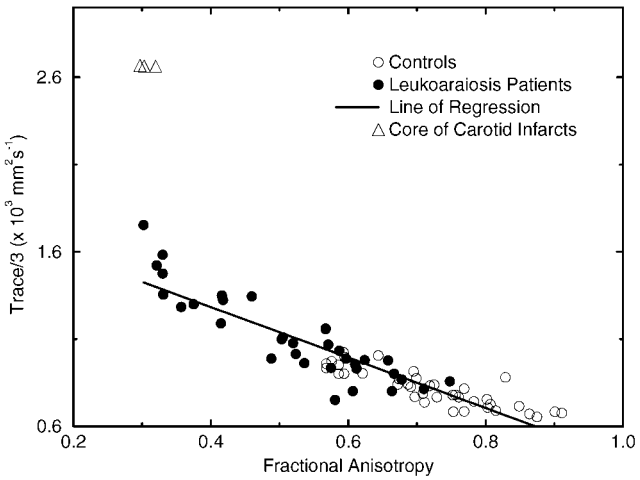

Figure 3. Relationship between mean diffusivity (trace/3) and fractional anisotropy (reproduced with permission from Jones *et al.*[19]) in patients with leukoaraiosis, controls and patients with infarcts secondary to carotid stenosis. The line of regression was derived from all points except for those from the patients with carotid stenosis

attributable to the proliferation of glial tissue in the leukoaraiotic patients, which would hinder diffusion.

CADASIL

CADASIL (cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy) is a recently recognized hereditary disease (linked to mutations of the *Notch 3* gene on chromosome 19), which results in subcortical ischaemic episodes and progressive dementia. In common with ischaemic leukoaraiosis, histological findings include pathological changes of small cerebral vessels, rarefaction of the white matter and increases in extra-cellular spaces. Furthermore, MR findings include diffuse T_2-weighted white matter hyperintensities.

Manka *et al.*[22] studied nine patients with CADASIL and nine age-matched controls with both diffusion and perfusion-weighted imaging. They observed significant increases in diffusivity in temporal white matter and frontal and parietal subcortical white matter, even in cognitively normal CADASIL patients with less pronounced leukoencephalopathies. However, they did not report any quantitative comparisons of cognitive function with diffusion characteristics.

In the first application of diffusion tensor imaging to CADASIL, Chabriat *et al.*[23,24] studied 16 symptomatic CADASIL patients (all with mutations on the *Notch 3* gene) and 10 age-matched controls; cognitive function was also assessed. The main finding was that mean diffusivity was increased both in regions of T_2-weighted hyperintensity ($1.15 \pm 0.15 \times 10^{-3}$ mm^2 s^{-1}) and in NAWM ($0.92 \pm 0.11 \times 10^{-3}$ mm^2 s^{-1}) compared with normal white matter in controls ($0.71 \pm 0.02 \times 10^{-3}$ mm^2 s^{-1}). The mean volume ratio,[25] which characterizes anisotropy, was higher both in regions of T_2-weighted hyperintensity (0.92 ± 0.04) and in NAWM (0.87 ± 0.07) compared with normal white matter in controls (0.68 ± 0.04). In common with the findings of Jones *et al.*[19] in ischaemic leukoaraiosis, there was a strong correlation ($r = 0.81$; $p = 0.0002$) between mean diffusivity and anisotropy in regions of T_2-weighted hyperintensity. In explaining the moderate increase in diffusion in NAWM and severe (60%) increase in white matter exhibiting T_2-weighted hyperintensities, Chabriat *et al.* suggested that the marked increase in diffusivity in regions of T_2-weighted hyperintensity was due to neuronal loss, while the mild increase in the NAWM was due to myelin loss. However, they were unable to say whether this myelin loss would be a secondary effect (i.e. Wallerian degeneration following small deep infarcts) or as a direct result of chronic ischaemia. Clearly, more work is needed in this area.

Another interesting finding of this study was a strong correlation between both mean diffusivity and anisotropy in regions of T_2-weighted hyperintensity and performance on cognitive tests, demonstrating a strong link between clinical severity and diffusion parameters. As the authors themselves pointed out, cognitive assessment was performed using global scales such as the MMSE scale and it will be interesting to investigate, using more specific cognitive testing, whether focal diffusion

Q2 changes are associated with focal cognitive or functional alterations.

AMYOTROPHIC LATERAL SCLEROSIS (ALS)

Amyotrophic lateral sclerosis (also known as motor neurone disease and Lou Gehrig's disease) is a fatal, progressive neuromuscular disease that attacks the motor neurons controlling voluntary movement. The result is wasting and atrophy of muscles, leading to difficulties in speaking or swallowing, stumbling, permanent fatigue and cramping, amongst other symptoms. The frequency is about 6 per 100 000. ALS can be broadly classified into two groups—bulbar onset and limb onset—depending on how symptoms first manifest themselves. The first symptoms of bulbar onset ALS include speaking and swallowing difficulties, resulting from degeneration of motor neurons concentrated in the brain stem (cortico-bulbar region). Limb onset patients experience first symptoms of ALS as muscle weakness in either the arms or legs. Limb onset patients eventually experience bulbar symptoms as the disease progresses.

The first study of ALS using diffusion-weighted imaging was by Segawa *et al.*[26] who, although observing differences in T_2—weighted images in ALS patients (i.e. hyperintense lesions), did not find any significant diffusion changes in the posterior limb of the internal capsule of ALS patients. Wu *et al.*[27] demonstrated hyperintensity in diffusion-weighted images (signifying reduced diffusivity) in the cortico-spinal tracts in 11 of 12 ALS patients and five of 12 controls. However, since diffusion-weighting was only applied in one direction (left–right) it is likely that this study was confounded by the effects of diffusion anisotropy.

In the first study to employ quantitative measurements of diffusivity and anisotropy in ALS, Ellis *et al.*[28] examined 11 subjects with limb-onset ALS, 11 with bulbar onset, and 20 age-matched controls with diffusion tensor MRI. Along the cortico-spinal tracts, mean diffusivity was found to be significantly increased ($p = 0.001$) in ALS patients (limb onset: 0.771×10^{-3} $mm^2\ s^{-1}$; bulbar onset: $0.778 \times 10^{-3}\ mm^2\ s^{-1}$) compared with controls ($0.732 \times 10^{-3}\ mm^2\ s^{-1}$). Fractional anisotropy was significantly reduced ($p = 0.007$) in bulbar onset subjects (0.726) compared with controls (0.773), but no significant difference was found between limb onset subjects (0.761) and controls.

Ellis *et al.* also demonstrated a positive correlation between mean diffusivity and disease duration ($r = 0.57$; $p = 0.009$) but no correlation with disease severity ($p > 0.29$) or upper motor neuron involvement. On the other hand, fractional anisotropy was found to correlate with measures of disease severity (assessed using the Ashworth spasticity scale and the ALS severity scale[29]). While there was no correlation between anisotropy and disease duration ($r = -0.17$; $p = 0.48$), significant correlations between anisotropy and the ALS severity scale ($r = -0.63$; $p = 0.003$) and Ashworth spasticity scale ($r = -0.56$; $p = 0.007$) existed.

ALZHEIMER'S DISEASE

Alzheimer's disease (AD) is a neurodegenerative disorder, generally considered to involve mainly the grey matter, although white matter cells such as axons and oligodendrocytes have been strongly implicated by histopathological studies.[30] General brain atrophy occurs, but temporal lobe structures and periventricular white matter including the corpus callosum have been seen to atrophy in recent MRI studies.[31]

Studies of AD have concentrated on changes in anisotropy associated with AD progression. By measuring diffusion in the corpus callosum at the mid-line, where axons are primarily oriented in the left-right direction, Hanyu *et al.*[32] were able to estimate changes in diffusion anisotropy simply by measuring diffusivity in the left–right and anterior–posterior (A-P) directions. They showed that, because of increased diffusivity in the A-P direction, the anisotropy was decreased in the genu and splenium of the corpus callosum in AD patients compared to age- and sex-matched controls. This was thought likely to be caused by axonal loss or demyelination in these areas, and the decrease was also correlated with the degree of cognitive impairment. In a separate study, Hanyu *et al.*[33] also examined temporal lobe white matter in the hippocampus and temporal stem. They again attempted to assess anisotropy, although because the white matter tracts were not aligned with any of the diffusion-encoding gradient directions, this study can only be regarded as semi-quantitative. Nevertheless, they showed a loss of anisotropy in the temporal lobe stem in suspected and probable AD patients that correlated strongly with the degree of cognitive impairment.

Rose *et al.*[34] compared the integrity of axonal tracts in those areas associated with cognitive function (the corpus callosum, superior longitudinal fasciculus and cingulum) with those associated with motor function (left and right internal capsule). Using the lattice index[25] as a measure of white matter tract integrity, they showed a preservation of the motor tract, but axonal degeneration in the 'cognitive' tracts. This is consistent with Wallerian degeneration of those axons that originate in the temporoparietal regions, brain areas that are generally affected in Alzheimer's disease.

CREUTZFELDT–JAKOB DISEASE

Creutzfeldt–Jakob disease (CJD) is a rare neurodegenerative disease, and to date no in-depth systematic studies of the diffusion-weighted appearance of CJD have been reported. However, there have been a handful of case

reports, and the common finding is of an increased conspicuity of abnormalities with DW imaging compared with T_2-weighted imaging.[35,36] Hyperintensities (reduced ADC values) are often seen around the basal ganglia with occasional further changes visible in lateral cortical areas.

Quantitative assessment in one study[35] showed modest reductions of around 15% in the ADC values in the basal ganglia. The cause of reduced diffusivity is unclear, although it was speculated that it could be related to the abnormal vacuoles in the cytoplasm that are found in the early stages of the neurodegenerative process.

HIV

Infection with the HIV has very recently been investigated by DTI. In a small cohort of 10 patients, Filippi and colleagues[37] assessed the mean diffusivity and anisotropy throughout the brain. Measurable differences in diffusion parameters were seen to correlate with viral load, leading the authors to speculate that DTI might be able to provide an early indicator of therapeutic effectiveness, even when conventional MR images appeared normal. Anisotropy changes in HIV were also seen in another similar study,[38] despite normal diffusivity and T_2 values; this is the first suggestion that a change in anisotropy might be a more sensitive indicator of abnormality in some diseases.

WHITE MATTER DISEASES IN CHILDREN

Krabbe disease (or globoid cell leukodystrophy) is an autosomal recessive disorder that occurs primarily in young children, predominantly affecting white matter of the CNS. Conventional MR findings include changes in periventricular white matter, the pyramidal tracts and white matter in the cerebellum and, as the disease progresses, white matter atrophy becomes more prominent.

Guo *et al.*[39] compared both T_2-weighted intensity and anisotropy measures in eight patients presenting with Krabbe disease to eight age-matched controls. They found significant differences in anisotropy between patients and controls in eight regions of white matter known to be affected by Krabbe disease, namely the middle cerebellar peduncle, internal capsule, genu and splenium of corpus callosum, frontal and parietal white matter, corona radiata and centrum semiovale. The authors also looked for changes in the cerebral peduncle, but found no significant differences in anisotropy there. They commented that, on visual inspection, it was only difficult to discern differences in anisotropy in the middle cerebellar peduncles and the cerebral peduncles, which they attributed to either the small size of these structures relative to the image resolution, or their proximity to CSF spaces, resulting in a partial volume effect. One of the main findings of this study was that the p-values for differences between patients and controls were consistently smaller (frequently by an order of magnitude) for diffusion anisotropy measurements than for T_2-weighted image intensity measurements. The authors therefore concluded that diffusion anisotropy is a more sensitive marker for detecting white matter abnormalities in Krabbe disease than conventional T_2-weighted imaging.

X-linked cerebral adrenoleukodystrophy (ALD) is another genetic disorder affecting the CNS. It is characterized by demyelination and inflammation, with a zonal nature in the brain lesions. Histopathologically, these zones correspond to demyelination with intact axons in the periphery of lesion; perivascular inflammation in addition to demyelination in an intermediate zone; and axonal loss, a mesh of glial fibrils and astrocytosis in the core of the lesions. Ito *et al.*[40] investigated ALD with DTI, showing a graded increase in diffusivity and reduction in diffusion anisotropy towards the centre of the MR-visible lesions, which they thought might correspond to the zones found on histology.[41]

CONCLUSIONS

Compared with other quantitative MRI techniques, tissue water diffusivity measurement has two potential advantages. First, its value is a physical property of the tissue being measured and, unlike T_1, T_2 and magnetization transfer, is not an MRI property. Thus, the values obtained should not depend on the details of the scanner used, such as the magnetic field strength. Secondly, the diffusion is encoded using magnetic field gradient pulses, and any imperfections in any RF pulses have a relatively minor impact on the accuracy of results. The magnetic field gradients are normally quite accurately calibrated (better than $\pm 1\%$ on all three axes) so that images are correctly sized; this then carries through into accurate diffusivity values and unbiased anisotropy measurements.

While some MRI parameters, such as the nuclear relaxation times, may well bear a relationship to the direction of the static polarizing field with respect to the tissue alignment,[42] in patient studies using solenoidal magnets, this direction is not usually a matter of choice. However, the diffusion-encoding magnetic field gradient can be applied in any arbitrary direction, allowing diffusion measurements to sample the directional dependence of diffusion in tissue. This allows inferences to be made about the shape and orientation of different types of cell, giving diffusion tensor MRI a unique advantage over other forms of MR image contrast. In white matter, where bundles of axons give healthy tissue a highly-ordered structure with an distinct direction of alignment, diseases that cause axons to degenerate and be replaced by more amorphous cells may give a definable signature on diffusion tensor MRI as the diffusion anisotropy is

reduced as a result. However, much more work is needed before we can start to draw firm conclusions about the relationships between tissue status and DTI appearance.

With the exception of acute stroke, which is not covered in this review, in many of the studies of the CNS that have so far exploited DW and DTI, changes in diffusivity have tended to mirror elevations in T_2-weighted intensity. It may be that the main advantage of diffusion imaging here is its quantitative nature: subtle changes in T_2 may go unnoticed, while the quantitative assessment offered by DTI may uncover them. However, we are now beginning to see the measures of anisotropy being used in many studies, where it may be possible to infer something about the degree of pathological damage particularly to white matter tracts, as the highly aligned axonal bundles are replaced either by extracellular space, or by other less ordered cells. It is here that DTI may add to our understanding of the pathophysiology of white matter diseases.

The newly emerging field of axonal fibre tracking from DTI data[43,44] may have a major impact on our understanding of the clinical manifestations of degenerative and inflammatory disease processes. Not only can a primary site of axonal injury be determined with DTI, but it may be that Wallerian degeneration[45] and perhaps even axonal pathways underpinning cortical remodelling could be visualised.

The more widespread deployment and clinical use of MRI scanners with strong magnetic field gradients capable of performing echo-planar diffusion-weighted sequences should see an increase in the clinical applications of this promising source of image contrast.

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