

## Progressive Supranuclear Palsy and Diffusion Tensor Imaging

Shoichi Ito

Associate Professor, The Office of Medical Education, Graduate School of Medicine, Chiba University, and Department of Neurology, Chiba University Hospital

DOI: 10.17925/ENR.2009.04.02.108

### Abstract

Progressive supranuclear palsy (PSP) is a neurodegenerative disease affecting multiple neural systems, particularly the extrapyramidal system. Early differentiation of PSP from other diseases mainly featuring parkinsonism, such as Parkinson's disease and multiple system atrophy, is necessary because the therapeutic strategy and outcome are substantially different. Diffusion tensor imaging is a recently developed magnetic resonance imaging (MRI) sequence that is able to non-invasively evaluate neural tracts. Two approaches may be used to measure diffusion properties. One approach is to measure diffusion properties by setting the regions of interest on circular/square regions or along the tractography. The other approach is to perform voxel-by-voxel analysis of the diffusion properties. There are several reports evaluating diffusion tensor abnormalities in PSP, and regions with diffusion tensor abnormalities are distributed through frontal projection fibres, the anterior part of the corpus callosum, superior longitudinal fasciculus, arcuate fasciculus, posterior thalamic radiations, internal capsule and superior cerebellar peduncles. Here, diffusion tensor studies in PSP are reviewed and clinical applications, limitations and future perspectives of diffusion tensor analysis in PSP are discussed.

### Keywords

Progressive supranuclear palsy, diffusion-weighted imaging, diffusion tensor imaging, tractography, statistical parametric mapping, apparent diffusion coefficient, fractional anisotropy, corpus callosum, superior longitudinal fasciculus, arcuate fasciculus, internal capsule, superior cerebellar peduncles

**Disclosure:** The author has no conflicts of interest to declare.

**Received:** 9 March 2009 **Accepted:** 21 July 2009

**Correspondence:** Shoichi Ito, 1-8-1 Inohana, Chuo-ku, Chiba, 260-8670, Japan. E: sito@faculty.chiba-u.jp

### Clinical Features of Progressive Supranuclear Palsy

Progressive supranuclear palsy (PSP) is a neurodegenerative disorder characterised by parkinsonism, supranuclear ophthalmoplegia, dysphagia and cognitive dysfunction. The National Institute of Neurological Disorders and Stroke (NINDS) PSP criteria are widely used for clinical diagnosis.<sup>1</sup> However, the clinical phenotypes of pathologically confirmed PSP patients are heterogeneous. Recently, PSP has been clinically classified into two phenotypes: Richardson's syndrome and PSP-parkinsonism.<sup>2</sup> Those patients who have Richardson's syndrome are neurologically characterised by the classic features, including the early onset of postural instability and falls, supranuclear vertical gaze palsy and cognitive dysfunction. PSP-parkinsonism is frequently misdiagnosed as Parkinson's disease in its early clinical stage and is characterised by asymmetrical onset, tremor and moderate initial therapeutic response to levodopa. Differentiating between Richardson's syndrome and Parkinson's disease is not difficult, but differentiating between PSP-parkinsonism and Parkinson's disease is occasionally challenging. Early differentiation of these diseases is necessary because the therapeutic strategy and outcome are substantially different (e.g. PSP patients have much worse prognosis).

### Diffusion-weighted Imaging

Magnetic resonance imaging (MRI) is a promising non-invasive tool that supports or complements clinical diagnosis. It is also useful for the

investigation of the pathophysiology of diseases. Recently, several new MRI techniques have been developed, and one of the most important of these tools is diffusion-weighted imaging,<sup>3</sup> which can be used to measure the diffusion of water molecules in the brain.<sup>4</sup> Brain diffusion is influenced by tissue density, neuronal axon and vessel direction and capillary flow. The apparent diffusion coefficient (ADC) or mean diffusivity (MD) is a parameter that represents diffusion intensity, and high ADC or MD values indicate increased diffusion intensity (see *Figure 1*). Diffusion intensities along three orthogonal directions are represented as  $\lambda_1$ ,  $\lambda_2$  and  $\lambda_3$ , and MD values are calculated as  $(\lambda_1 + \lambda_2 + \lambda_3)/3$ . Axial diffusivity ( $\lambda_1$ ) and radial diffusivity  $(\lambda_2 + \lambda_3)/2$  are occasionally used as additional measures to identify whether differences in anisotropy may be caused by diffusion parallel or perpendicular to the white-matter fibres, respectively. Cytotoxic oedema is a typical pathological condition in which decreased ADC values are indicative of cerebral infarction<sup>5,6</sup> or other conditions. ADC values are increased by vasogenic oedema<sup>7</sup> or demyelination.<sup>8</sup> In neurodegenerative diseases, ADC values are increased in affected areas because of disruption of neuronal axons.<sup>9,10</sup>

### Diffusion Tensor Imaging

Diffusion tensor imaging was introduced as a new imaging modality in 1994.<sup>11</sup> Molecules inside neuronal axons have a low probability of crossing the myelin membrane, and thus brain diffusion in this modality is usually anisotropic. Fractional anisotropy (FA) provides an

index of brain anisotropy; the FA values are calculated as a value from zero to one, with a score of one representing tissue that is more anisotropic (see *Figure 2*).

The posterior limbs of the internal capsule, cerebral peduncles, corpus callosum, optic radiations and middle cerebellar peduncles are representative anisotropic tissues, whereas the grey matter, including the cerebral cortices and basal ganglia, are less anisotropic (see *Figure 2*).<sup>12</sup> The development of diffusion tensor imaging enables brain diffusion to be measured in multiple directions (see *Figure 3*) and the FA in each direction to be calculated for each voxel.<sup>13</sup> Diffusion tensor tractography is a recently developed method to visualise the neuronal fibres in 3D by computing the connections of diffusion tensor in adjacent voxels (see *Figure 4*).<sup>14</sup>

### Measuring Diffusion Properties

Two approaches may be used to measure and analyse diffusion properties such as ADC and FA values. One approach is to measure diffusion properties by setting the regions or voxels of interest, which are classically defined as circular or square regions, in each subject. Regions of interest can be set along the tractography ('tract of interest'), and the diffusion properties in entire voxels on a particular neuronal pathway can be measured.<sup>15</sup> The other approach is to perform voxel-by-voxel analysis of the diffusion properties. The statistical parametric mapping method is an algorithm that is generally used in neuroimaging studies, and whole brain analysis can be performed without the subjective dispersion of setting regions of interest.<sup>16</sup> Appropriate normalisation, segmentation into white matter and smoothing of diffusion images on specific software are necessary for performing voxel-by-voxel diffusion analysis.

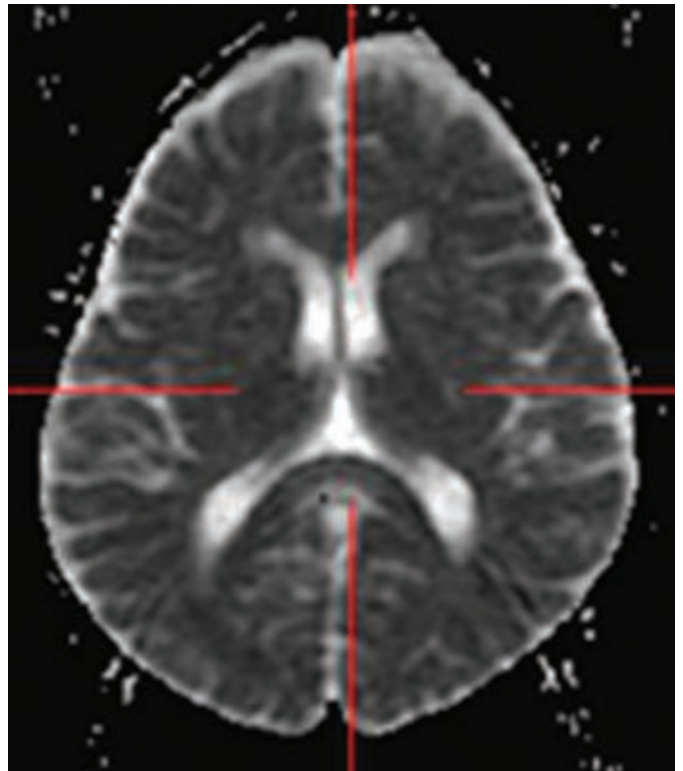
### Diffusion Tensor Abnormalities in Progressive Supranuclear Palsy Supratentorial Structures

Padovani et al. were the first to perform diffusion tensor analysis in patients with early PSP.<sup>17</sup> They conducted voxel-by-voxel analysis of diffusion tensor images using statistical parametric mapping, combined with grey-matter analysis using optimised voxel-based morphometry.<sup>18</sup> Their study revealed decreased FA values in the superior longitudinal fasciculus, anterior part of the corpus callosum, arcuate fasciculus, posterior thalamic radiations and internal capsule (see *Table 1*), in addition to decreased FA values in the affected grey matter, including the premotor cortex, frontal operculum, anterior insula, hippocampus, and parahippocampal gyrus, the pulvinar, dorsomedial and anterior nuclei of the thalamus and the superior and inferior colliculus.

These results are suggestive of frontal dominant grey- and white-matter cerebral damage, and are compatible with previous diffusion and morphometric studies.<sup>19,20</sup> Nilsson et al. reported a visual reduction of cortical projection fibres in patients with PSP in 3D diffusion tensor tractography on 3 Tesla MRI.<sup>21</sup>

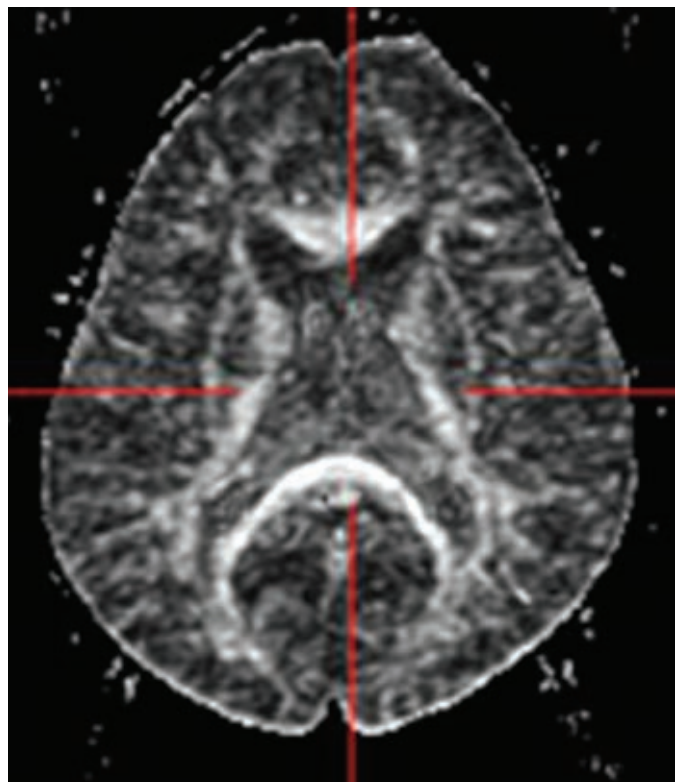
Recently, we analysed the corpus callosum as a representative area of cerebral commissure fibres by diffusion tensor imaging<sup>22</sup> using a new partitioning method for the human corpus callosum.<sup>23</sup> The results showed that the FA values were significantly decreased in CC1 (the prefrontal area) and CC2 (the premotor and supplementary motor areas), and the ADC values were significantly increased in CC1 and CC2. Receiver operating characteristic analysis showed excellent

**Figure 1: An Apparent Diffusion Coefficient (ADC) Map Shows Relative Homogeneous ADC Values in the Brain Parenchyma**



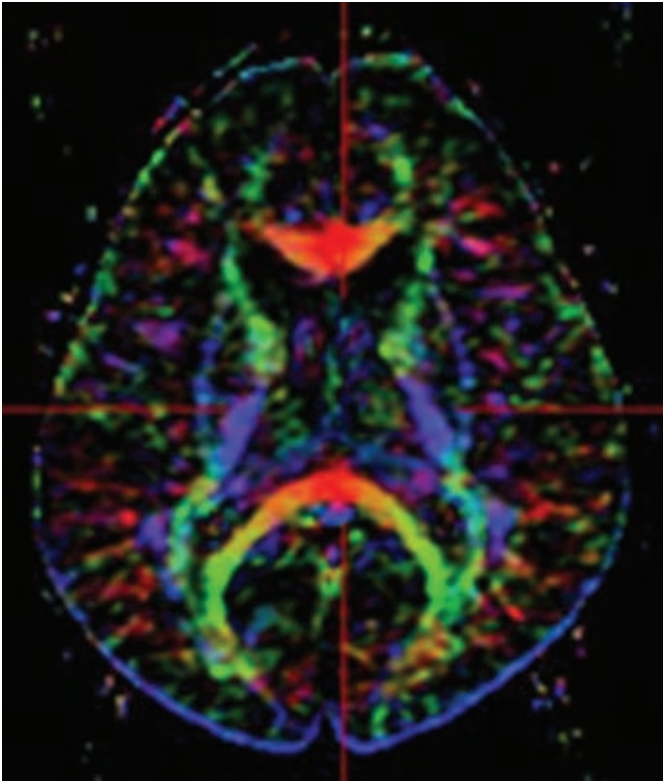
*Image obtained from normal subject.*

**Figure 2: A Fractional Anisotropy (FA) Map Shows High FA Values in the Posterior Limbs of the Internal Capsule, Genu and Splenium of the Corpus Callosum and Optic Radiations**



*Image obtained from normal subject.*

**Figure 3: Colour-coded Fractional Anisotropy Map**



The colour-coded fractional anisotropy (FA) map depicts left-to-right orientated fibres as red (e.g. corpus callosum), anterior-to-posterior fibres as green (e.g. optic radiations) and inferior-to-superior fibres as blue (e.g. pyramidal tracts).

**Figure 4: Diffusion Tensor Tractography of the Entire Corpus Callosum**



Commissure fibres running through the genu and rostrum of the corpus callosum are shown in red, those running through the body of the corpus callosum are shown in pink, purple, blue and dark blue and those in the splenium of the corpus callosum are shown in light blue.

reliability of FA and ADC analyses of CC1 for differentiating PSP from Parkinson's disease. Although FA values generally decrease and ADC values increase during the normal ageing process in the frontal white matter and anterior corpus callosum,<sup>24-29</sup> our results showed differences in diffusion parameters between age-matched PSP patients and normal subjects. Our results suggest that the frontal commissure fibres are preferentially damaged in patients with PSP, and thus diffusion tensor imaging of the corpus callosum is helpful for the diagnosis of PSP.

**Table 1: Distribution of Diffusion Tensor Abnormalities Observed in Progressive Supranuclear Palsy**

Supratentorial Structures
Cortical projection fibres
Anterior part of the corpus callosum*
Superior longitudinal fasciculus
Arcuate fasciculus
Posterior thalamic radiations
Internal capsule
Infratentorial Structures
Superior cerebellar peduncles

\*Commissure fibres connecting the prefrontal, premotor and supplementary motor areas.

### Infratentorial Structures

Blain et al. reported diffusion changes in the brainstem in patients with PSP and multiple system atrophy using a region-of-interest approach.<sup>30</sup> They revealed increased MD values in the decussation of superior cerebellar peduncles in patients with PSP, in contrast to decreased FA values in the middle cerebellar peduncles and increased MD values in the pons in patients with multiple system atrophy (MSA). Nilsson et al. also showed the same distribution of diffusion abnormalities in patients with PSP and MSA using diffusion tensor tractography on 3 Tesla MRI.<sup>21</sup> These results showed that cerebellar efferent fibres (superior cerebellar peduncles) are preferentially affected in patients with PSP, whereas cerebellar afferent fibres (pons and middle cerebellar peduncles) are damaged in patients with multiple system atrophy.

### Clinical Application and Limitations of Diffusion Tensor Imaging in Progressive Supranuclear Palsy

Diffusion tensor imaging is a feasible method for investigating human white-matter conditions. However, it is not fully practical for differentiating PSP from other parkinsonisms such as Parkinson's disease or multiple system atrophy because there are some overlaps of diffusion parameters between PSP and other forms of parkinsonism.<sup>22,30</sup> Analysis using statistical parametric mapping is not applicable for individual cases unless the Z score of diffusion parameters can be calculated for each selected area, and this requires specialised software and training.<sup>17</sup> In visual inspection of diffusion tensor tractography images,<sup>21</sup> it is difficult to set a cut-off line of abnormalities of fibre visualisation. In summary, diffusion tensor analysis is not essential for the diagnosis of PSP, although it can be an additional test for further confirmation of the diagnosis.

### Future Perspectives of Diffusion Tensor Analysis in Progressive Supranuclear Palsy

To the best of my knowledge, there has been no detailed correlation analysis between clinical features and diffusion tensor parameters in PSP. Frontal diffusion abnormalities probably reflect clinical frontal lobe dysfunction in conceptualisation, mental flexibility, motor programming, sensitivity to interference, inhibitory control and environmental autonomy for executive functions. Diffusion tensor analysis regarding supranuclear ophthalmoplegia, which is a core feature of PSP, is also necessary for further understanding of the pathophysiology of PSP.

Conventional diffusion tensor imaging using echo planar technique is generally insufficient for detailed analysis of the brainstem because of a strong susceptibility effect around the skull base. Diffusion tensor

imaging using a line scan technique<sup>31</sup> may be feasible for analysing the brainstem in patients with PSP.<sup>32,33</sup> Finally, the clinical subtypes of PSP, Richardson's syndrome and PSP-parkinsonism<sup>2</sup> have not yet been investigated by diffusion tensor imaging.

Early differentiation of these subtypes of PSP is important for planning a clinical strategy because the treatment responses and disease outcome are different. Diffusion tensor imaging is a feasible method for investigating brain conditions in PSP. ■



Shoichi Ito is an Associate Professor in the Office of Medical Education at the Graduate School of Medicine at Chiba University and in the Department of Neurology at Chiba University Hospital. His primary interests are clinical practice, research and education in neurology and neuroradiology, and more specifically include diagnosis using computed tomography (CT) and magnetic resonance imaging (MRI) and neurodegenerative diseases and spinal cord diseases.

- Litvan I, Agid Y, Calne D, et al., Clinical research criteria for the diagnosis of progressive supranuclear palsy (Steele-Richardson-Olszewski syndrome): report of the NINDS-SPSP international workshop, *Neurology*, 1996;47: 1–9.
- Williams DR, de Silva R, Paviour DC, et al., Characteristics of two distinct clinical phenotypes in pathologically proven progressive supranuclear palsy: Richardson's syndrome and PSP-parkinsonism, *Brain*, 2005;128:1247–58.
- Le Bihan D, Breton E, Lallemand D, et al., MR imaging of intravoxel incoherent motions: application to diffusion and perfusion in neurologic disorders, *Radiology*, 1986;161: 401–7.
- Schaefer PW, Grant PE, Gonzalez RG, Diffusion-weighted MR imaging of the brain, *Radiology*, 2000;217:331–45.
- Chien D, Kwong KK, Gress DR, et al., MR diffusion imaging of cerebral infarction in humans, *AJNR Am J Neuroradiol*, 1992;13:1097–1102; discussion 1103–95.
- Moseley ME, Kucharczyk J, Mintorovitch J, et al., Diffusion-weighted MR imaging of acute stroke: correlation with T2-weighted and magnetic susceptibility-enhanced MR imaging in cats, *AJNR Am J Neuroradiol*, 1990;11:423–9.
- Schwartz RB, Mulkern RV, Gudbjartsson H, Jolesz F, Diffusion-weighted MR imaging in hypertensive encephalopathy: clues to pathogenesis, *AJNR Am J Neuroradiol*, 1998;19:859–62.
- Castriota Scanderbeg A, Tomaiuolo F, Sabatini U, Nocentini U, et al., Demyelinating plaques in relapsing-remitting and secondary-progressive multiple sclerosis: assessment with diffusion MR imaging, *AJNR Am J Neuroradiol*, 2000;21:862–8.
- Della Nave R, Foresti S, Tessa C, et al., ADC mapping of neurodegeneration in the brainstem and cerebellum of patients with progressive ataxias, *Neuroimage*, 2004;22: 698–705.
- Stahl R, Dietrich O, Teipel SJ, Hampel H, et al., White matter damage in Alzheimer disease and mild cognitive impairment: assessment with diffusion-tensor MR imaging and parallel imaging techniques, *Radiology*, 2007;243:483–92.
- Basser PJ, Mattiello J, LeBihan D, MR diffusion tensor spectroscopy and imaging, *Biophys J*, 1994;66:259–67.
- Shimony JS, McKinstry RC, Akbudak E, et al., Quantitative diffusion-tensor anisotropy brain MR imaging: normative human data and anatomic analysis, *Radiology*, 1999;212: 770–84.
- Le Bihan D, Mangin JF, Poupon C, et al., Diffusion tensor imaging: concepts and applications, *J Magn Reson Imaging*, 2001;13:534–46.
- Melhem ER, Mori S, Mukundan G, et al., Diffusion tensor MR imaging of the brain and white matter tractography, *AJR Am J Roentgenol*, 2002;178:3–16.
- Taoka T, Iwasaki S, Sakamoto M, et al., Diffusion anisotropy and diffusivity of white matter tracts within the temporal stem in Alzheimer disease: evaluation of the "tract of interest" by diffusion tensor tractography, *AJNR Am J Neuroradiol*, 2006;27:1040–45.
- Richardson MP, Friston KJ, Sisodiya SM, et al., Cortical grey matter and benzodiazepine receptors in malformations of cortical development. A voxel-based comparison of structural and functional imaging data, *Brain*, 1997;120 (Pt 11):1961–73.
- Padovani A, Borroni B, Brambati SM, et al., Diffusion tensor imaging and voxel based morphometry study in early progressive supranuclear palsy, *J Neurol Neurosurg Psychiatry*, 2006;77:457–63.
- Good CD, Johnsrude IS, Ashburner J, et al., A voxel-based morphometric study of ageing in 465 normal adult human brains, *Neuroimage*, 2001;14:21–36.
- Brenneis C, Seppi K, Schocke M, et al., Voxel based morphometry reveals a distinct pattern of frontal atrophy in progressive supranuclear palsy, *J Neurol Neurosurg Psychiatry*, 2004;75:246–9.
- Ohshita T, Oka M, Imon Y, et al., Apparent diffusion coefficient measurements in progressive supranuclear palsy, *Neuroradiology*, 2000;42:643–7.
- Nilsson C, Markenroth Bloch K, Brockstedt S, et al., Tracking the neurodegeneration of parkinsonian disorders – a pilot study, *Neuroradiology*, 2007;49:111–19.
- Ito S, Makino T, Shirai W, Hattori T, Diffusion tensor analysis of corpus callosum in progressive supranuclear palsy, *Neuroradiology*, 2008;50:981–5.
- Hofer S, Frahm J, Topography of the human corpus callosum revisited – comprehensive fiber tractography using diffusion tensor magnetic resonance imaging, *Neuroimage*, 2006;32:989–94.
- Abe O, Aoki S, Hayashi N, et al., Normal aging in the central nervous system: quantitative MR diffusion-tensor analysis, *Neurobiol Aging*, 2002;23:433–41.
- Camara E, Bodammer N, Rodriguez-Fornells A, Tempelmann C, Age-related water diffusion changes in human brain: a voxel-based approach, *Neuroimage*, 2007;34:1588–99.
- Pfefferbaum A, Adalsteinsson E, Sullivan EV, Frontal circuitry degradation marks healthy adult aging: Evidence from diffusion tensor imaging, *Neuroimage*, 2005;26:891–9.
- Salat DH, Tuch DS, Greve DN, et al., Age-related alterations in white matter microstructure measured by diffusion tensor imaging, *Neurobiol Aging*, 2005;26:1215–27.
- Salat DH, Tuch DS, Hevelone ND, et al., Age-related changes in prefrontal white matter measured by diffusion tensor imaging, *Ann N Y Acad Sci*, 2005;1064:37–49.
- Sullivan EV, Adalsteinsson E, Pfefferbaum A, Selective age-related degradation of anterior callosal fiber bundles quantified in vivo with fiber tracking, *Cereb Cortex*, 2006;16: 1030–39.
- Blain CR, Barker GJ, Jarosz JM, et al., Measuring brain stem and cerebellar damage in parkinsonian syndromes using diffusion tensor MRI, *Neurology*, 2006;67:2199–2205.
- Gudbjartsson H, Maier SE, Mulkern RV, Morocz IA, et al., Line scan diffusion imaging, *Magn Reson Med*, 1996;36: 509–19.
- Yen K, Weis J, Kreis R, et al., Line-scan diffusion tensor imaging of the posttraumatic brain stem: changes with neuropathologic correlation, *AJNR Am J Neuroradiol*, 2006;27: 70–73.
- Nagata M, Maeda M, Tsukahara H, et al., Brain stem hypertensive encephalopathy evaluated by line scan diffusion-weighted imaging, *AJNR Am J Neuroradiol*, 2004;25:803–6.