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ORIGINAL COMMUNICATION

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Combined MR spectroscopic imaging and diffusion tensor MRI visualizes corticospinal tract degeneration in amyotrophic lateral sclerosis

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Abstract Motor neuron damage and cortical spinal tract (CST) degeneration are pathological features of amyotrophic lateral sclerosis (ALS). We combined whole-brain diffusion tensor imaging (DTI) and three-dimensional magnetic resonance spectroscopic imaging (MRSI) to study the CST at different locations. Eight ALS patients were compared with normal controls. Fractional anisotropy (FA) and mean diffusivity (MD), and the ratio of N-acetyl-aspartate (NAA) to creatine (Cr) were measured at various locations in the CST, including the subcortical white matter (SWM), centrum semiovale (CS), periventricular white matter (PV), posterior limb of the internal capsule (PIC) and cerebral peduncle (CP). Patients showed significantly lower FA than controls in the CST, including the SWM, CS, PV and PIC. Although there was a trend towards elevated MD in ALS patients, this did not reach statistical significance. NAA/Cr ratios were also decreased in ALS patients compared with normal controls, with significant differences in the SWM and PV but not in PIC. Combined whole-brain DTI and MRSI can detect axonal degeneration in ALS. Measurements of FA obtained in the SWM, CS, PV and PIC, and NAA/Cr ratios in the SWM and PV yield the most robust results.

Key words amyotrophic lateral sclerosis · corticospinal tract · magnetic resonance imaging · nuclear magnetic resonance · echo planar imaging

Introduction

Amyotrophic lateral sclerosis (ALS) is the most common motor neuron disease. This devastating neurodegenerative disorder of unknown origin is characterized by degeneration and loss of the motor neurons in the spinal cord, brainstem, and cerebral cortex, and associated with damage to the corticobulbar and corticospinal tracts (CST) [1, 2]. Clinically, sporadic ALS is manifested by muscle weakness, wasting, spasticity, and weight loss. Death usually occurs within 2–5 years after the onset of symptoms. Currently, there is no technique to objectively and quantitatively assess the extent of upper motor neuron damage. Diagnosis is based on the El Escorial clinical criteria, electrophysiological findings, and exclusion of other conditions [3, 4].

Conventional magnetic resonance imaging (MRI) has been applied to the diagnosis of ALS, with limited success [5–8]. More recently, attention has focused on proton MR spectroscopy to provide a metabolic marker of upper motor neuron involvement [9–16]. Diffusion tensor imaging (DTI) is a novel magnetic resonance method that makes use of multiple non-collinear diffusion sensitizing gradients to study the movement of molecular water. DTI indices that may be obtained include mean diffusivity (MD), which measures the magnitude of water diffusion independent of direction, and

fractional anisotropy (FA), which quantifies the directionality of water diffusion [17, 18]. Exploiting the principles of anisotropy (the preferential diffusion of water along fiber tracts), these quantitative markers may be useful in the study of the function and microstructural integrity of white matter [17, 18]. DTI has been successfully applied to the study of cerebral ischemia, multiple sclerosis, brain tumors [19–21], and ALS [22–24]. However, there have been no previous studies using both whole-brain DTI and magnetic resonance spectroscopic imaging (MRSI) to examine ALS patients. We therefore combined studies of the CST in ALS patients using these novel MR techniques, and compare these parameters at different locations along the CST.

Materials and methods

Patients

Eight patients with clinically definite ALS based on El Escorial criteria [3, 4] attending the PLA General Hospital neurology service were studied. The mean age of ALS patients was 45.75 ± 7.94 years, with a median duration of symptoms of 15.63 months (range 6–25); there were 4 men and 4 women. Twelve healthy age-matched controls (mean age: 45.08 ± 11.73 years, 8 men and 4 women) were included in the DTI study; a second group of non-matched volunteers without neurological disease (mean age: 43.8 ± 16.72, 3 men and 2 women) was analysed for MRSI. Informed consent was obtained from all subjects before entry into the study.

MRI protocols

All MR studies were performed on a 1.5 T Signa Twinspeed MRI system (General Electric, Milwaukee, USA). All patients and volunteers underwent fast spin-echo T2-weighted (TR 3600 ms, TE 102 ms; matrix size 128x256; FOV 240 mm; 28x6 mm axial slices), and fluid attenuated inversion recovery (TI = 2200 ms) studies. Patients and DTI volunteers underwent diffusion-weighted protocol comprising single-shot echo-planar imaging (TR 8000 ms, TE 70 ms; acquisition matrix 128x128; FOV 24 cm; b values 0 and 1000 s/mm^2, applied along 25 non-collinear directions). Each section was 6 mm thick, with 0.5m gap.

Patients and MRSI volunteers underwent localized three-dimensional multi-voxel proton spectroscopic imaging. Point-resolved spectroscopy (PRESS) sequence localization was used (TR 1500 ms, TE 136 ms, one excitation) to acquire a single volume acquisition of an 80 mm cube. The localizer volume was selected to include the CST and avoid scalp contamination. The total acquisition time for all sequences was approximately 60 minutes.

Data analysis

Two observers (HY, CCTL), who were blinded to the clinical details, analysed the conventional MRI, DTI and MRSI studies by consensus reading on Advantage Windows workstation (Functool, General Electric, Milwaukee, USA). In each subject, CST white matter was studied at 5 anatomical locations: subcortical white matter (SWM) below the precentral gyrus, centrum semiovale (CS), periventricular white matter (PV), posterior limb of the internal capsule (PIC), and cerebral peduncle (CP), were analysed. On conventional MRI, the presence or absence of abnormal signal intensity in the CST and precentral gyrus was noted; other focal areas of signal abnormality were also recorded.

Post-processing of DTI data was carried out using a pixel-by-pixel method to calculate fractional anisotropy (FA) and mean diffusivity (MD). Elliptical regions of interest (ROIs) of uniform size (20–30 mm^2) were placed in the CST as visualized on the b = 0 (T2-weighted) images bilaterally, 10 regions in all. Care was taken to place the ROIs along the CST to minimize partial volume effects from surrounding non-CST regions. These ROIs were automatically propagated to the FA and MD maps by the manufacturer's software, which recorded these values.

Individual MRSI voxels with nominal dimensions of 15 x 15 x10 mm were placed in the CS, PV, PIC guided by the same b = 0 images obtained from the DTI dataset. Semi-quantitative spectral measurements of peak heights of N-acetyl aspartate (NAA) and creatine (Cr), were obtained, followed by calculation of the metabolite ratio NAA/Cr. Again, results of voxels on both sides were summed. Examples of MRSI voxel and ROI placement on FA and MD maps are shown in Fig. 1.

Comparison of means of FA, MD, and NAA/Cr between groups was performed using the Mann-Whitney test for independent samples, followed by comparisons at different locations along the CST. Statistical significance was established at $p < 0.05$.

Results

There were six ALS patients with limb onset disease and two with bulbar onset; average duration of disease was of 15.63 ± 6.53 months. Conventional MRI studies in four of eight ALS patients showed foci of high signal in the PIC on T2 or FLAIR images, two patients had subcortical white matter hyperintensities and two had abnormalities in the CP. No patient had abnormal findings of low signal intensity in the precentral gyrus. Five of 12 normal volunteers had bilateral foci of high signal in the PIC on T2-weighted images and one had an abnormality in the subcortical white matter.

The differences in combined and regional DTI and MRSI parameters are shown in Table 1. ALS patients had significantly lower FA (0.44 ± 0.09) than controls (0.50 ± 0.08, p = 0.001), MD values were also higher in patients (7.75 ± 0.25 x 10^{-4} mm^2/s) than controls (7.58 ± 0.22 x 10^{-4} mm^2/sec) although this difference did not reach significance (p = 0.189). Regional FA differences were significant in the SWM, CS, PV, and PIC, but not the CP.

In our MRSI study, we could not consistently obtain measurements from the precentral gyrus in all subjects owing to technical difficulties near the scalp. Similarly, measurements in the brainstem were discarded because of inability to place the ROI in the correct anatomical location. Hence, only the SWM, PV and PIC were studied. The combined NAA/Cr ratio was significantly lower in ALS patients (1.94 ± 0.19) than normal controls (2.20 ± 0.34, p = 0.002). Within the CST, the difference between patients and controls was significant at the SWM and PV but not at the PIC.

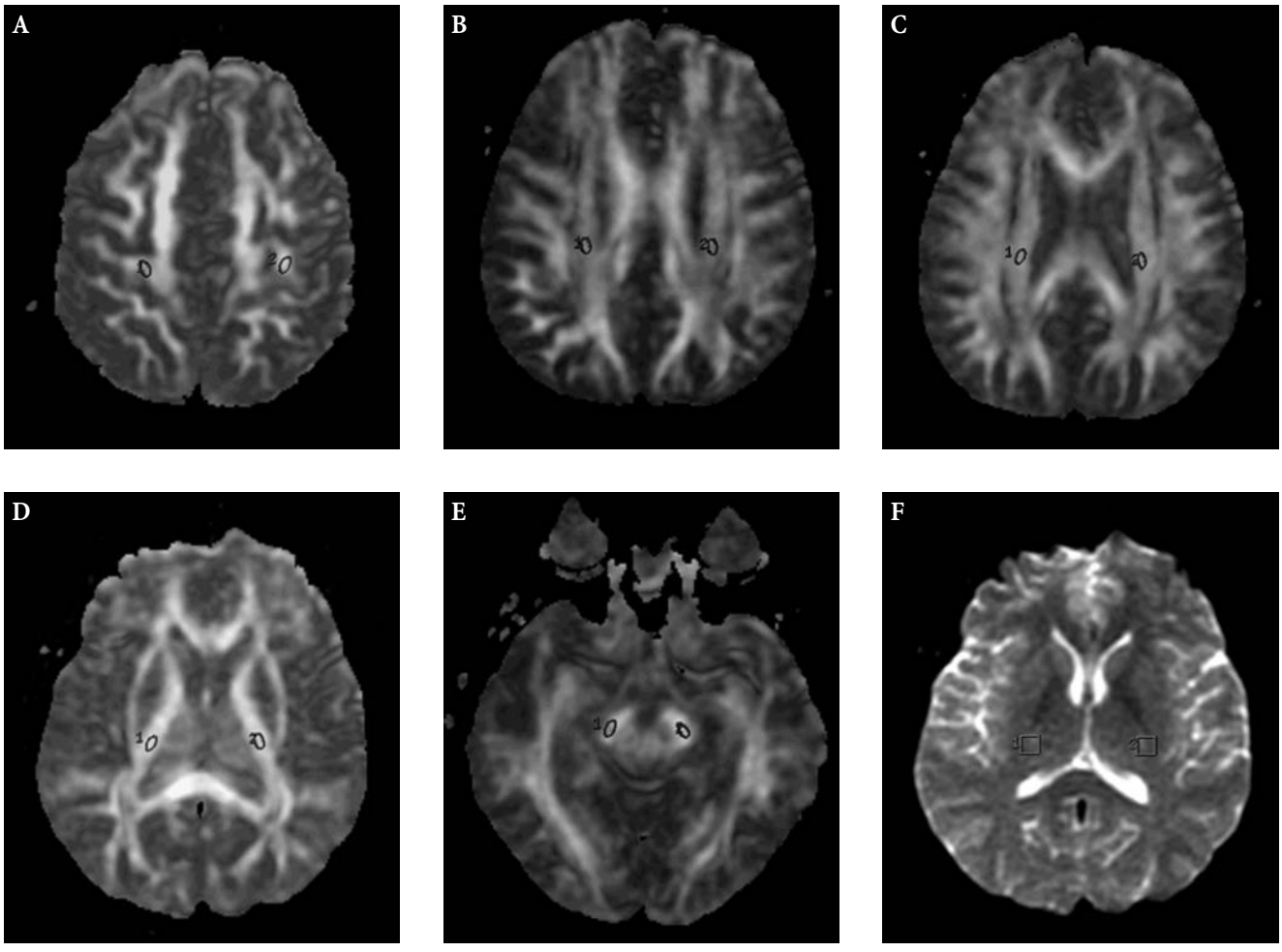

Fig. 1 Axial MR images from a patient with ALS showing location of regions of interest in the corticospinal tracts. Fractional anisotropy (FA) maps from (**A**) subcortical white matter (SWM); (**B**) centrum semiovale (CS); (**C**) periventricular white matter (PV); (**D**) posterior limb of internal capsule (PIC); and (**E**) cerebral peduncle (CP). (**F**) T-2 weighted (b = 0) image shows MRSI voxel placement within the PIC

Discussion

ALS affects both upper and lower motor neurons. Histopathological examination has revealed degeneration and motor neuron death in both the cortical gray matter and white matter tract throughout the CST. Mutations in superoxide dismutase, free radicals, increased lipofuscin granules in the motor neurons, and apoptosis have been implicated in disease pathogenesis [7, 25, 26].

Neuron and axonal damage may be detected as abnormal signal intensity in the areas of the motor cortex and along the CST. T2-weighted MRI studies have shown decreased signal intensity in the precentral gyrus, as well as increased signal intensity in the CST [5–8]. These findings may be more prominent and more frequently seen on FLAIR sequences [27, 28]. On T2-weighted and FLAIR MRI, none of our patients had precentral gyral abnormality, and only half had abnormal findings in the CST. Similar signal changes were also present in a smaller percentage of normal controls. Our results are in agreement with previous reports, which have shown that hyperintensity in the CST was not specific for ALS; ischemic disease, vitamin B12 deficiency and Friedrich's ataxia may also cause similar findings on MRI [29, 30]. Other studies have also found bilaterally symmetrical, sharply defined foci of high signal in the PIC in neurologically normal controls [31–33]. In these individuals, hyperintense foci in the PIC may be due to the presence of large fibers with thick myelin sheaths in the CST [34].

The poor sensitivity and overlapping appearances on qualitative MRI has led to interest in DTI and MRSI as quantitative markers of ALS. Using seven non-collinear diffusion directions, Ellis et al. found reduced FA and elevated MD in the posterior limbs of the internal capsule in ALS patients [22]. In that study, the PIC was studied on a single section in the coronal plane, and compared with sex-matched controls. Our study, using 25 diffusion

Table 1 DTI and MRSI parameters in the corticospinal tracts

Regions	Mean FA controls	+ SD	Mean FA ALS Patients	+ SD	Z	p
All locations	0.50	0.08	0.44	0.09	−3.24	0.001*
SWM	0.41	0.05	0.36	0.04	−2.24	0.025*
CS	0.41	0.03	0.36	0.03	−2.55	0.011*
PV	0.53	0.04	0.45	0.06	−2.78	0.005*
PIC	0.58	0.03	0.52	0.06	−2.70	0.007*
CP	0.54	0.06	0.52	0.04	−0.97	0.335
Regions	**Mean MD controls**	**+ SD**	**Mean MD ALS Patients**	**+ SD**	**Z**	**p**
MD all locations	7.58	0.22	7.75	0.25	−1.31	0.189
MD SWM	7.15	0.27	7.37	0.33	−1.70	0.090
MD CS	7.44	0.27	7.63	0.27	−1.51	0.132
MD PV	7.41	0.23	7.50	0.30	−0.58	0.563
MD PIC	7.26	0.23	7.45	0.34	−0.81	0.418
MD CP	8.65	0.72	8.79	0.70	−0.62	0.537
Regions	**Mean NAA/Cr controls**	**+ SD**	**Mean NAA/Cr ALS Patients**	**+ SD**	**Z**	**p**
NAA/Cr all locations	2.20	0.34	1.94	0.19	−3.15	0.002*
NAA/Cr SWM	2.46	0.24	2.08	0.19	−2.49	0.013*
NAA/Cr PV	2.12	0.15	1.85	0.19	−2.49	0.013*
NAA/Cr PIC	1.88	0.27	1.63	0.24	−1.61	0.107

* Significantly different at $p < 0.05$
MD is expressed in units of $x10^{-4}$ mm^2/s

directions, extends this initial work and examines regional differences along the course of the CST, from the subcortical region down to the cerebral peduncles, ten regions in all.

Among ALS patients in our study, FA was significantly lower, but despite the trend towards higher MD, the difference did not reach statistical significance when compared with normal controls. Our observations may reflect the early phase of axonal degeneration, during which decreased diffusion directionality results in decreased FA, but before disrupted cellular integrity or increased extracellular space occurs to give rise to elevated MD [35]. The shorter duration of symptoms (mean 15.63 months in our patients and 32.9 and 26.1 months in limb and bulbar onset patients respectively), may contribute to the disparity between our findings and those of the previous study [22]. Such a combination of decreased FA without significant elevation of MD has also been observed in the normal appearing white matter in cerebral infarction [19] and multiple sclerosis [20]. In these studies the observations were attributed to Wallerian degeneration of the axons and myelin. Our findings raise the possibility that FA may be more sensitive than MD in some patient populations with axonal degeneration, and this may have future clinical applications, particularly in the early stage of the disease. However, our small sample size was a limiting factor, and larger studies with longitudinal comparisons of FA and MD as functions of duration and severity of ALS might help resolve this issue.

In our study of regional variation in FA along the CST, we found differences between patients and controls in all regions of the CST except the CP. Technical difficulties caused by partial volume effect of multiple fiber tracts, perhaps compounded by sphenoid airspace susceptibility effects degrading measurements in the brainstem, may be responsible for the lack of significance in the differences in the cerebral peduncles. With multiple readings at different locations, we expect the accuracy and confidence to improve on a study taking only a single measurement.

NAA/Cr ratios were significantly decreased in ALS patients compared with controls. In prior studies using single-voxel methods and two-dimensional MRSI, a decrease in NAA concentration or NAA/Cr ratio had been detected in the precentral gyrus [9–14, 36, 37]. Multivoxel techniques analyse metabolic information as an array of spectra with smaller voxel sizes, and hence have better spatial resolution than single-voxel methods. Anatomical coverage is also superior, and multiple locations within the CST may be studied with a single three-dimensional MRSI acquisition.

Our analysis of different locations in the CST showed that the NAA/Cr ratio in the SWM and PVD were significantly different in ALS patients, but the differences in the PIC failed to reach statistical significance. In a study

of the PIC in ALS patients, Schuff et al. also found normal NAA concentration but increased choline in the PIC [37]. They postulated that there may be disproportionately fewer losses of subcortical motor neuron fibers than of cortical motor neurons. However, this does not adequately explain our significant results in the SWM and PV. In our combined study, there was difficulty in obtaining an exact anatomical match between MRSI and DTI within the same patient. These technical limitations, as well as the larger voxel of interest in MRSI when compared to DTI, may also contribute to our failure to find a significant difference in the PIC on MRSI. Perhaps technical improvements such as absolute metabolite quantification [9–11, 37], or using other metabolite markers such as glutamate at short echo times [15] might be a more suitable parameter to study ALS patients at the PIC level.

In conclusion, our experience suggests that in ALS patients with non-specific conventional MRI findings, combined whole-brain DTI and MRSI may be useful for detecting neuronal damage in the CST. To yield the most robust and consistent results, FA measurements may be taken along the CST with the exception of the cerebral peduncles, and spectroscopic measurement of NAA/Cr should be obtained from the subcortical white matter and periventricular white matter, but not the posterior limb of the internal capsule. Further studies need to be done with larger groups of patients before recommending these markers of upper motor neuron damage in ALS. Such quantitative methods have the potential to be used as surrogate markers to measure disease progression, which would be helpful in clinical trials to assess treatment efficacy.

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References

1. Leigh PN (1993) Pathogenic mechanisms in amyotrophic lateral sclerosis and other motor neuron disorders. In: Calne DB, ed. Neurodegenerative Diseases. Philadelphia: Sannders, pp 473–488
2. Hirano A (1991) Cytopathology of amyotrophic lateral sclerosis. Adv Neurol 56:91–101
3. Brooks BR (1994) El Escorial World Federation of Neurology criteria for the diagnosis of amyotrophic lateral sclerosis. Subcommittee on Motor Neuron Diseases/Amyotrophic Lateral Sclerosis of the World Federation of Neurology Research Group on Neuromuscular Diseases and the El Escorial "Clinical limits of amyotrophic lateral sclerosis" workshop contributors. J Neurol Sci 124(Suppl):96–107
4. Brooks BR, Miller RG, Swash M, Munsat TL (2000) El Escorial revisited: revised criteria for the diagnosis of amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord 1:293–299
5. Goodin DS, Rowley HA, Olney RK (1988) Magnetic resonance imaging in amyotrophic lateral sclerosis. Ann Neurol 23:418–420
6. Oba H, Araki T, Ohtomo K, Monzawa S, Uchiyama G, Koizumi K, Nogata Y, Kachi K, Shiozawa Z, Kobayashi M (1993) Amyotrophic lateral sclerosis: T2 shortening in motor cortex at MR imaging. Radiology 189:843–846
7. Cheung G, Gawel MJ, Cooper PW, Farb RI, Ang LC, Gawal MJ (1995) Amyotrophic lateral sclerosis: correlation of clinical and MR imaging findings. Radiology 194:263–270
8. Hofmann E, Ochs G, Pelzl A, Warmuth-Metz M (1998) The corticospinal tract in amyotrophic lateral sclerosis: an MRI study. Neuroradiology 40:71–75
9. Bowen BC, Pattany PM, Bradley WG, Murdoch JB, Rotta F, Younis AA, Duncan RC, Quencer RM (2000) MR imaging and localized proton spectroscopy of the precentral gyrus in amyotrophic lateral sclerosis. AJNR Am J Neuroradiol 21:647–658
10. Gredal O, Rosenbaum S, Topp S, Karlsborg M, Strange P, Werdelin L (1997) Quantification of brain metabolites in amyotrophic lateral sclerosis by localized proton magnetic resonance spectroscopy. Neurology 48:878–881
11. Pohl C, Block W, Traber F, Schmidt S, Pels H, Grothe C, Schild HH, Klockgether T (2001) Proton magnetic resonance spectroscopy and transcranial magnetic stimulation for the detection of upper motor neuron degeneration in ALS patients. J Neurol Sci 190:21–27
12. Pioro EP, Antel JP, Cashman NR, Arnold DL (1994) Detection of cortical neuron loss in motor neuron disease by proton magnetic resonance spectroscopic imaging in vivo. Neurology 44:1933–1938
13. Block W, Karitzky J, Traber F, Pohl C, Keller E, Mundegar RR, Lamerichs R, Rink H, Ries F, Schild HH, Jerusalem F (1998) Proton magnetic resonance spectroscopy of the primary motor cortex in patients with motor neuron disease: subgroup analysis and follow-up measurements. Arch Neurol 55: 931–936
14. Ellis CM, Simmons A, Andrews C, Dawson JM, Williams SC, Leigh PN (1998) A proton magnetic resonance spectroscopic study in ALS: correlation with clinical findings. Neurology 51:1104–1109
15. Pioro EP, Majors AW, Mitsumoto H, Nelson DR, Ng TC (1999) 1H-MRS evidence of neurodegeneration and excess glutamate + glutamine in ALS medulla. Neurology 53:71–79
16. Chan S, Shungu DC, Douglas-Akinwande A, Lange DJ, Rowland LP (1999) Motor neuron diseases: comparison of single-voxel proton MR spectroscopy of the motor cortex with MR imaging of the brain. Radiology 212:763–769
17. Basser PJ, Pierpaoli C (1996) Microstructural and physiological features of tissues elucidated by quantitative-diffusion-tensor MRIJ Magn Reson B 111:209–219
18. Pierpaoli C, Basser PJ (1996) Toward a quantitative assessment of diffusion anisotropy. Magn Reson Med 36: 893–906
19. Werring DJ, Toosy AT, Clark CA, Parker GJ, Barker GJ, Miller DH, Thompson AJ (2000) Diffusion tensor imaging can detect and quantify corticospinal tract degeneration after stroke. J Neurol Neurosurg Psychiatry 69:269–272
20. Ciccarelli O, Werring DJ, Wheeler-Kingshott CA, Barker GJ, Parker GJ, Thompson AJ, Miller DH (2001) Investigation of MS normal-appearing brain using diffusion tensor MRI with clinical correlations. Neurology 56: 926–933

21. Mori S, Frederiksen K, van Zijl PC, Stieltjes B, Kraut MA, Solaiyappan M, Pomper MG (2002) Brain white matter anatomy of tumor patients evaluated with diffusion tensor imaging. Ann Neurol 51:377–380
22. Ellis CM, Simmons A, Jones DK, Bland J, Dawson JM, Horsfield MA, Williams SC, Leigh PN (1999) Diffusion tensor MRI assesses corticospinal tract damage in ALS. Neurology 53:1051–1058
23. Toosy AT, Werring DJ, Orrell RW, Howard RS, King MD, Barker GJ, Miller DH, Thompson AJ (2003) Diffusion tensor imaging detects corticospinal tract involvement at multiple levels in amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry 74:1250–1257
24. Jacob S, Finsterbusch J, Weishaupt JH, Khorram-Sefat D, Frahm J, Ehrenreich H (2003) Diffusion tensor imaging for long-term follow-up of corticospinal tract degeneration in amyotrophic lateral sclerosis. Neuroradiology 45: 598–600
25. Shaw PJ, Ince PG, Falkous G, Mantle D (1995) Oxidative damage to protein in sporadic motor neuron disease spinal cord. Ann Neurol 38:691–695
26. Trotti D, Rolfs A, Danbolt NC, Brown RH Jr, Hediger MA (1999) SOD1 mutants linked to amyotrophic lateral sclerosis selectively inactivate a glial glutamate transporter. Nat Neurosci 2:427–433
27. Hecht MJ, Fellner F, Fellner C, Hilz MJ, Heuss D, Neundorfer B (2001) MRI-FLAIR images of the head show corticospinal tract alterations in ALS patients more frequently than T2-, T1- and proton-density-weighted images. J Neurol Sci 186:37–44
28. Zhang L, Ulug AM, Zimmerman RD, Lin MT, Rubin M, Beal MF (2003) The diagnostic utility of FLAIR imaging in clinically verified amyotrophic lateral sclerosis. J Magn Reson Imaging 17: 521–527
29. Peretti-Viton P, Azulay JP, Trefouret S, Brunel H, Daniel C, Viton JM, Flori A, Salazard B, Pouget J, Serratrice G, Salamon G (1999) MRI of the intracranial corticospinal tracts in amyotrophic and primary lateral sclerosis. Neuroradiology 41:744–749
30. Miaux Y, Martin-Duverneuil N, Cognard C, Weill A, Chiras J (1994) Areas of high signal intensity in the posterior limbs of the internal capsules in amyotrophic lateral sclerosis: normal or pathologic MR finding? Radiology 191:870–871
31. Hajnal JV, De Coene B, Lewis PD, Baudouin CJ, Cowan FM, Pennock JM, Young IR, Bydder GM (1992) High signal regions in normal white matter shown by heavily T2-weighted CSF nulled IR sequences. J Comput Assist Tomogr 16:506–513
32. Mirowitz S, Sartor K, Gado M, Torack R (1989) Focal signal-intensity variations in the posterior internal capsule: normal MR findings and distinction from pathologic findings. Radiology 172:535–539
33. Yoshiura T, Higano S, Rubio A, Shrier DA, Kwok WE, Iwanaga S, Numaguchi Y (2000) Heschl and superior temporal gyri: low signal intensity of the cortex on T2-weighted MR images of the normal brain. Radiology 214:217–221
34. Yagishita A, Nakano I, Oda M, Hirano A (1994) Location of the corticospinal tract in the internal capsule at MR imaging. Radiology 191:455–460
35. Barnes D, Munro PM, Youl BD, Prineas JW, McDonald WI (1991) The long-standing MS lesion. A quantitative MRI and electron microscopic study. Brain 114(Pt 3):1271–1280
36. Suhy J, Miller RG, Rule R, Schuff N, Licht J, Dronsky V, Gelinas D, Maudsley AA, Weiner MW (2002) Early detection and longitudinal changes in amyotrophic lateral sclerosis by (1)H MRSI. Neurology 58:773–779
37. Schuff N, Rooney WD, Miller R, Gelinas DF, Amend DL, Maudsley AA, Weiner MW (2001) Reanalysis of multislice (1)H MRSI in amyotrophic lateral sclerosis. Magn Reson Med 45: 513–516