Diffusion tensor imaging of radiculopathy in patients with lumbar disc herniation

PRELIMINARY RESULTS

Aims

The aim of this study was to evaluate the time course of changes in parameters of diffusion tensor imaging (DTI) such as fractional anisotropy (FA) and apparent diffusion coefficient (ADC) in patients with symptomatic lumbar disc herniation. We also investigated the correlation between the severity of neurological symptoms and these parameters.

Patients and Methods

A total of 13 patients with unilateral radiculopathy due to herniation of a lumbar disc were investigated with DTI on a 1.5T MR scanner and underwent micro discectomy. There were nine men and four women, with a median age of 55.5 years (19 to 79). The changes in the mean FA and ADC values and the correlation between these changes and the severity of the neurological symptoms were investigated before and at six months after surgery.

Results

The mean FA values were significantly lower (p = 0.0005) and mean ADC values were significantly higher (p = 0.0115) in compressed nerves than in intact nerves. Although the FA values increased significantly at six months after surgical treatment (p = 0.020), the ADC values decreased but not significantly (p = 0.498). There were strong correlations between the DTI parameters such as the FA value and the severity of the neurological symptoms as assessed using the Japanese Orthopaedic Association (JOA) score and the Roland-Morris Disability Questionnaire (RDQ).

Conclusion

This preliminary study suggests that it may be possible to use DTI to diagnose, quantitatively evaluate and follow-up patients with lumbar nerve entrapment.

Take home message: DTI is a potential tool for functional diagnosis of lumbar nerve damage.

Cite this article: Bone Joint J 2016;98-B:387–94.

Lumbar nerve entrapment leads to low back and leg pain. However discrepancies between the symptoms and the degree of nerve root compression as seen on conventional MRI are frequently found. Abnormalities within the discs may be seen on MRI in the asymptomatic population,1,2 making it difficult to understand the cause of the pain or to provide a quantitative evaluation of nerve damage.

Diffusion-weighted imaging (DWI) can provide valuable information about the micro-structure of tissues. This is done by applying a motion-probing gradient (MPG) in certain directions to monitor the random movement of water molecules within tissues.3–5 DWI has been widely used in the evaluation of the central nervous system especially for the diagnosis of focal brain ischaemia.6 It may also be used in the diagnosis of multiple sclerosis5 and myelopathy due to cervical spondylosis.5 Data from DWI can be used to determine quantitative diffusion values such as the apparent diffusion coefficient (ADC) and increases in the mean diffusivity (MD) values have been observed in injured nerves undergoing demyelination.6,7

Yamashita et al and Takahara et al10–12 have demonstrated the feasibility of whole-body MR neurography using DWI which can identify tissues with impeded diffusion, such as tumours involving the brain, spinal cord, and peripheral nerves. With an approximate ten minute scan time on a 1.5T scanner, MR neurography using DWI can image lumbar nerve roots. The mean ADCs in nerve root compression with foraminal stenosis13 and lumbar disc...
which reflects the direction of molecular diffusion. FA to determine a scalar fractional anisotropy (FA) value. This is because the axonal cell membrane and the myelin sheath in nerve fibres prevent diffusion in the direction which is perpendicular to their fascicles, resulting in the isotropy of the diffusion of water molecules being lost. This is diffusion anisotropy and selectively recording this information is diffusion tensor imaging (DTI) and tractography. DTI is the only method which can give an indirect view of the microstructure of nervous tissue in addition to the pathway of the fibres. The diffusion data can be used to determine a scalar fractional anisotropy (FA) value which reflects the direction of molecular diffusion. FA values range from zero to one, with high values indicating anisotropic diffusion and low values indicating more isotropic diffusion. DTI may be used for the evaluation and visualisation of peripheral nerves and the measurement of axonal regeneration in mice and rat sciatic nerves. A decrease in mean FA values occurs in injured nerves undergoing demyelination.

Imaging of the spinal cord is challenging due to its relatively small size, artefacts arising from tissue-bone interfaces and motion artifacts from respiration. We have shown that DTI of the lumbar nerves allows both visualisation and quantification of their entrapment in patients with foraminal stenosis using MRI at 3.0T. There are, however, few reports of using DTI to assess a lumbar nerve root and there have been no previous studies of the changes in DTI after surgical treatment nor of the correlation between the severity of neurological symptoms and DTI parameters in patients with radiculopathy.

In this study we have evaluated the time course of FA and ADC values after surgery and investigated the correlation between these changes and symptoms in patients with radiculopathy caused by lumbar disc herniation.

**Patients and Methods**

**Patients.** The study includes 13 patients; nine men and four women with a median age of 55.5 years (19 to 79) who were treated by micro endoscopic discectomy for unilateral radiculopathy and lumbar disc herniation between April 2013 and April, 2014. All patients underwent DTI scanning before and after surgery. The patients gave informed consent and the study had prior approval from the Chiba University and the Shimoshizu National Hospital ethics committee. The diagnosis was based on neurological symptoms, selective nerve root infiltration and plain radiographs, CT and MRI. The location of the symptomatic nerves in the 13 patients were, one at L2, one at L3, five at L4, five at L5, and one at S1. Exclusion criteria included: bilateral symptoms and polyradiculopathy, lumbar canal stenosis and previous surgery to the lumbar spine. The mean duration of sciatica before MRI was 38 days (14 to 58). In 12 patients, quantitative evaluations were followed up by DTI at six months after the operation. Symptoms were evaluated using straight-leg-raising (SLR), muscle wasting and the sensory disturbance. Neurological severity was assessed using a visual analogue scale (VAS) score for low back pain and leg pain from 100 (extreme pain) to zero (no pain), numbness in the leg from 100 (extreme numbness) to zero (no numbness), the Japanese Orthopaedic Association (JOA; 0 to 29 points) scoring system, and the Roland-Morris Disability Questionnaire (RDQ; 0 to 24 point). The normal JOA score is 29 points, based on three subjective symptoms (nine points), three clinical signs including straight-leg raising (six points), and seven activities of daily living (14 points) (Table I).

The normal RDQ is 0 points with the total number of items checked from a minimum of 0 to a maximum of 24.

Clinical assessment was undertaken at presentation and six months after surgery (Table II).

**MRI protocol.** A 1.5-T MRI scanner (Philips Medical Systems, Philips Electronics Japan, Achieva 1.5T Nova Dual) was used in this study. Sagittal T1-weighted (TR/TE, 400/14), axial and sagittal T2-weighted fast spin-echo (TR/TE, 4000/102) sequences were obtained using a 256 × 256 matrix, 260 mm field of view (FOV), and 3/1 mm slice thickness/gap.

The DTI series were acquired using Spectral presaturation with inversion recovery (SPIR), and an echo-planar imaging (EPI) sequence with a free-breathing scanning technique. Patients were scanned in a supine position using a SENSE-Spine-coil. The following imaging parameters were set: 800 s/mm² b-value, MPG: 15 directions, 10000/71 ms for TR/TE respectively, axial slice orientation, 3/0 mm slice thickness/gap, 320 213 mm field of view (FOV), 96 × 192 matrix, 3.3 × 1.66 × 3.0 mm³ actual voxel size, 1.6 × 1.6 × 4.0 mm³ calculated voxel size, four excitations, 50 total slices, 10 min 31 s scan time.

**Image analysis.** Tractography and FA mapping were analysed using Volume One (http://www.volume-one.org/) and dTVIISR (diffusion TENSOR Visualiser II, the Second Release; http://www.ut-radiology.umin.jp/people/masutani/dTV.htm) software. The diffusion tensor was calculated using a log-linear fitting method. The regions of interest (ROIs) were placed at three levels at 3 mm intervals distal to the site of compression of the nerve by the disc herniation on the axial image of ADC and FA maps and their mean values were calculated by the software (Fig. 1). The size of the ROIs from 25 mm² to 50 mm² was selected to be as precise as possible on the respective nerve roots to avoid partial volume effects when the mean FA was calculated. CSF contamination effects were low because the thickness of the slices was 3mm smaller than the size of the L5 dorsal root ganglion, which was 5 mm in width and 10mm in length. All DTI analyses were performed by two trained spinal surgeons (YE, YO), with experience in DTI analysis of the nerve roots. Each observer recorded the FA and ADC values twice to measure inter- and intra-observer variation.
Statistical analysis. Statistical analyses were performed with Stat View software (version 5.0, SAS institute, Cary, North Carolina). A post hoc test was used to compare the FA and ADC values of the nerve roots at the level of the compression between the entrapped and intact sides in the same patient. Comparisons of these values at this level before and after surgery in the same patient were also performed. All values were presented as the mean and standard deviation (SD). Pearson correlation coefficients were calculated to determine the correlation between DTI parameters and symptoms such as VAS score, JOA score, and RDQ. The inter-intra-observer variation were analysed with Pearson correlation coefficients. A threshold of p < 0.05 was considered significant.

Results
The mean FA and ADC values are shown in Figure 2. The mean FA values were significantly lower (p < 0.001) and the mean ADC values were significantly higher (p < 0.05) in compressed nerves than in intact nerves.

The time course changes in the mean FA and ADC values in the involved nerve are shown in Figure 3. Although FA
values were increased significantly at 6 months after surgical treatment (p < 0.05), ADC values decreased but this difference was not significant (p = .4980).

The correlations between DTI parameters are shown in Figure 4 and Table III with the mean FA and ADC values correlated to the symptoms such as JOA score, and RDQ. There was a strong correlation between the FA and the JOA score (r = 0.797, p < 0.05) and RDQ (r = -0.731, p < 0.05) (Figs 4a and 4b). There was a strong correlation between the ADC and the JOA score (r = -0.646, p < 0.05) and RDQ (r = 0.744, p < 0.01) (Figs 4c and 4d). There was also a strong correlation between ADC and numbness after the operation (r = 0.715, p < 0.05) (Fig. 4e).

In the analysis of the ADC values, observer variations were not found. The inter- and intra-observer variations were r = 0.83 and r = 0.74, respectively (p = 0.011). In the analysis of FA value, observer variations were also not found. The inter- and intra-observer variations were r = 0.95 and r = 0.89, respectively (p = 0.0008).

Tractography of the lumbar nerves in a 46-year-old man with disc herniation at L5/S1 before and after surgery is shown in Figure 5. Tractography of the S1 nerve elongated to the proximal side indicated that it correlated with the neurological improvement.

Discussion
Lumbar radicular pain due to disc herniation was described by Mixter and Barr in 1934. It has recently been suggested that the dorsal root ganglion has a role in the pathogenesis of sciatic pain. Olmarker et al. reported that compression caused oedema and demyelination in the spinal nerve roots of the cauda equina in pigs. The redundant nerve roots above the level of severe extradural compression have been evaluated in morphological and histological studies of patients with severe spinal stenosis. The pathological changes in these redundant roots included demyelination and loss of axons. In the ventral roots, degenerative changes were located within the redundant portion of the nerves and extended caudally from the constriction. In the dorsal roots, degenerative changes occurred within the redundant portions of the nerves and extended cranially to the constricted...
canal.\textsuperscript{31} Using CT myelograms, Takata et al\textsuperscript{32} reported that disc herniation caused widespread oedema throughout the nerve root. Toyone et al\textsuperscript{33} using gadolinium-DTPA-enhanced MRI showed enhancement of the symptomatic nerve roots in patients with a herniated lumbar disc and that the degree of enhancement reflected the severity of the sciatica. Kobayashi et al\textsuperscript{34} and Jinkins\textsuperscript{35} have attributed this enhancement to a breakdown of the blood–nerve barrier.

MacDonald et al\textsuperscript{18} used a mouse brain injury model and showed that relative anisotropy and axial diffusivity were reduced by six hours to four days after trauma, corresponding to axonal injury; from one to four weeks after trauma, relative anisotropy remained decreased, whereas radial diffusivity increased, corresponding to demyelination, edema, and persistent axonal injury. Beaulieu reported that Wallerian degeneration after peripheral nerve injury reduced the anisotropy of water diffusion.\textsuperscript{4,5}

Conventional MRI using T1- and T2-weighted imaging can neither selectively visualise peripheral nerves nor quantitatively assess the severity of the nerve lesion. It is not possible to predict which patients with a large central disc prolapse compressing the nerve roots are going to deteriorate neurologically nor how rapidly.\textsuperscript{36} DTI is a non-invasive method of tracing the nerve fibre bundles...
effectively and evaluating the nerve injury quantitatively. It has also been used in tractography on the lumbar nerve root.\textsuperscript{20-25} In this study, we showed that the lumbar nerve roots were clearly visualised with tractography; FA was decreased and ADC increased in the symptomatic nerve root. Although FA increased significantly after microdiscectomy, ADC values were decreased but not significantly. Increased ADC may be due to inflammation or oedema, whereas decreased FA may reflect damaged tissue, demyelination, axonal loss or an increase in isotropic water volume. ADC increased post-operatively, suggesting persistent inflammation or oedema in patients in whom there was persistent numbness in the leg.

There were strong correlations between the DTI parameters of FA and ADC and indices of neurological severity due to inflammation or oedema, whereas decreased FA may reflect damaged tissue, demyelination, axonal loss or an increase in isotropic water volume. ADC increased post-operatively, suggesting persistent inflammation or oedema in patients in whom there was persistent numbness in the leg.

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Graphs showing the correlations between DTI parameters (FA and ADC values) and clinical symptoms such as JOA score and RDQ and leg numbness. There was a strong correlation between FA values and JOA score ($r = 0.797$, $p = 0.011$) and RDQ ($r = -0.731$, $p = 0.011$) (a). There was a strong correlation between ADC values and JOA score ($r = -0.646$, $p = 0.0356$) and RDQ ($r = 0.744$, $p = 0.0079$) (b). There was a strong correlation between the ADC value and leg numbness after operation ($r = 0.716$, $p = 0.0124$) (c).

\textbf{Fig. 4a}

\textbf{Fig. 4b}

\textbf{Fig. 4c}

\textbf{Fig. 4d}

\textbf{Fig. 4e}
using the JOA score and RDQ. Gao et al.\textsuperscript{37} reported that FA values were positively correlated with JOA scores in patients with myelopathy due to cervical spondylosis, which was consistent with our findings.

Electrophysiology has been used to analyse neural function but it is invasive. Recently we found that there were no abnormalities in either amplitude or nerve conduction velocity in the tibial or peroneal nerves in patients with L5 foraminal stenosis.\textsuperscript{38} Nerve conduction studies are tests that are used to detect nerve conduction disorders peripheral to the knee, but lumbar nerve injuries are localised to the spinal canal, and if Waller degeneration does not extend to the region below the knee, then there is the possibility of false-negative findings. The changes in DTI parameters indicating neuropathy were dependent on the site of nerve compression. DTI may reveal the local lumbar nerve damage.\textsuperscript{38}

There are several limitations to this study. First, only a few patients were investigated. Secondly, the six month follow-up was short. Thirdly, tractography is mathematical modeling of the diffusion tensor data using probability theories to assess the most likely course of diffusion and the number of tracts visualised by DTI. It does not present the actual volume of nerve fibre trajectories. Fourthly, there was no control group. We have previously described the use of DWI in patients with lumbar disc herniation who have not undergone surgery, showing that ADC values increased in the involved nerve, but the differences between the changes noted before and after the onset of sciatica were not significant.\textsuperscript{12} Fifthly, although we measured DTI parameters without a reference source, measurements need to be normalised to an internal or external standardised phantom.

In conclusion, we found that the FA values were decreased significantly in the symptomatic nerves and subsequently increased at six months after surgery, which correlated well with JOA and RDQ scores. The ADC values increased significantly in symptomatic nerves after surgery and showed a gradual but non-significant decrease at six months which also correlated with JOA and RDQ scores. DTI of the compressed root is different from that of the uncompressed root and parameters such as FA can predict neurological severity, thus making it a potential tool for the functional diagnosis of lumbar nerve damage.

Author contributions:
Y. Eguchi: Project development, data collection, manuscript writing.
Y. Oikawa: Project development.
S. Orita: Data collection.
K. Yamauchi: Data collection.
M. Suzuki: Data collection.
Y. Aoki: Data collection.
A. Watanabe: MRI methodology.
K. Takahashi: The scientific guarantor of this manuscript.

\begin{table}[h]
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\caption{Symptoms}
\begin{tabular}{|l|l|l|}
\hline
Clinical symptoms & p-value  \\
\hline
FA & JOA score & p = 0.011 \\
    & RDQ & p = 0.011 \\
ADC & JOA score & p = 0.0356 \\
    & RDQ & p = 0.0079 \\
ADC (post-operatively) & Leg numbness (post-operatively) & p = 0.0124 \\
\hline
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References