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SCIENTIFIC ARTICLE

Diffusion tensor imaging of diabetic amyotrophy

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Abstract

Objective To qualitatively and quantitatively characterize the nerves of patients with diabetic amyotrophy (DA) using magnetic resonance neurography (MRN) with diffusion tensor imaging (DTI).

Materials and methods Forty controls and 13 DA cases were analyzed. 1.5-Tesla and 3.0-Tesla MRN with DTI was used. Qualitative data from 13 patient records were recorded. Region of interest (ROI) measurements were taken of bilateral L3 through S2 lumbosacral nerve roots, femoral nerves, and sciatic nerves. An ANOVA and multiple linear regression analysis were performed. An intraclass correlation coefficient (ICC) was calculated between two readers.

Results In DA cases, abnormalities of the lumbosacral nerve roots ($n = 11$ patients), sciatic ($n = 10$), femoral ($n = 13$), and obturator nerves ($n = 4$) were seen; denervation changes of the abdominopelvic muscles were also identified. Quantitatively, minimum and mean nerve signals on B600 were significantly less than controls ($p < 0.001$). Minimum and mean ADC values were significantly greater in cases than in controls ($p < 0.001$ and $p = 0.002$ respectively). Mean fractional anisotropy (FA) values were significantly lower in cases than in controls ($p = 0.041$). There were no significant differences in the minimum FA values between cases and controls. Minimum and mean ADCs correlated positively with highest recorded hemoglobin A1 (HbA1c) while controlling for sex, age, and BMI ($\beta = 0.518$, $p < 0.001$ and $\beta = 0.302$, $p = 0.020$ respectively). ICCs were 0.892 (B600), 0.717 (ADC), and 0.730 (FA).

Conclusion Neuromuscular lesions secondary to DA are qualitatively and quantitatively identified on MRN with DTI, and a positive correlation of ADC levels with serum HbA1c levels exists. Thus, MRN with DTI can be employed as a non-invasive diagnostic tool, if DA is suspected.

Keywords Magnetic resonance imaging · Diabetic amyotrophy · Lumbosacral plexus · Diabetic neuropathies · Diffusion tensor imaging

Introduction

Diabetes is a frequent chronic disease with a prevalence of 12.2% in adults [1]. Diabetic patients suffer from comorbidities that are either provoked or complicated by their long-standing diagnosis, accounting for the associated increased risk of death [1, 2]. The effective healthcare burden is substantial, with an estimated cost of $327 billion in 2017 [3].

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The pathophysiology of diabetic peripheral neuropathy (DPN) is controversial. Current understanding suggests that several factors, including intraneural deposition of advanced glycosylation end products, cause neurovascular damage. Diabetic amyotrophy (DA) is a proximal, rather than distal, neuropathy of the lumbosacral (LS) plexus. Unlike DPN, there has been no demonstrated relationship between DA severity and hemoglobin A1C (HbA1C) levels [4, 5]. Furthermore, the pathophysiology of DA is no longer thought to be like that in DPN, but is instead an inflammatory mediated process [6].

Diabetic amyotrophy may present in any number of ways, but typically does so as unilateral pain and/or weakness affecting the proximal muscles of the lower limbs [4]. Symptoms of DA may masquerade as other common etiologies (e.g., joint disease, disc disease, radiculopathy, and other pathological conditions affecting the LS plexus) as the clinical signs are relatively nonspecific. The diagnosis typically relies on an

extensive workup and is usually made clinically by the exclusion of other common diagnoses. Electrophysiology and conventional MRI of the lumbar spine or pelvis are commonly used in this domain; however, with some caveats. Electrophysiology causes discomfort to the patient, and results can be affected by any number of variables, some of which include pH, body temperature, or patient habitus [7–10]. It is often challenging to localize the exact site of neuropathy on electrophysiology. MRI may provide useful information by exclusion of the regional organic lesions or significant spine disease. However, the derived images are often limited in nerve characterization owing to lower resolution and contrast in addition to vascular signal contamination [11–13].

With poor glucose control, peripheral nerves may develop neuropathic findings, which are observed as hyperintensity and/or thickening of the lumbar nerve roots and/or their peripheral branches on magnetic resonance neurography (MRN) [14, 15]. The magnitude of such findings has been shown to correlate with the severity of neuropathic symptoms. Intraneural fatty change in the chronic stages of neuropathy has also been suggested [13]. MRN provides substantial benefit over conventional MRI in the observation of nerve architecture and pathological conditions [16]. Its utility in the identification of DPN lesions has been previously reported [14, 15, 17, 18]. There has been successful demonstration of the use of diffusion-weighted imaging in DPN in previous studies with quantitation of neuropathy in the lower legs [18, 19]. However, exploration of diffusion-weighted and diffusion tensor imaging (DTI) has not been performed in DA. The authors sought to characterize the neuromuscular lesions using DTI in this case–control study. We hypothesized that DA can be quantitatively distinguished from controls using DTI parameters, i.e., fractional anisotropy (FA) and the apparent diffusion coefficient (ADC).

Materials and methods

This is a retrospective cross-sectional evaluation following the HIPAA and institutional IRB guidelines. IRB approval was obtained, and informed consent was waived.

Patients and controls

Control group: an electronic search of the medical records from the university hospital and its affiliated county hospital yielded 40 consecutive patients with normal MRN findings of the LS and the surrounding muscles (31 October 2014 through 18 April 2018). The search identified studies performed for suspected genitofemoral or pudendal neuralgia as these nerves are rarely affected by diabetes. All studies included institutional DTI protocol as described below. Exclusion criteria included an existing diagnosis of diabetes or pre-diabetes, suspected radiculopathy, abnormal findings in the LS plexus and its distal branches (obturator, femoral, sciatic), abnormal muscle findings, surgical hardware of the spinal column, and poor image quality. Five patients were excluded owing to the presence of diabetes or pre-diabetes, and 4 patients because of metal in the field of view. The subject age, sex, body mass index (BMI), and field strength of MRN were recorded.

Lesion (DA) group: an electronic search of the medical records from the university hospital and its affiliated county hospital yielded 13 DA patients who had received MRN LS plexus studies (15 July 2013 through 20 February 2018) with the same imaging protocol and met both inclusion (final diagnosis of DA) and exclusion criteria. Exclusion criteria included no final diagnosis of diabetes or pre-diabetes, surgical hardware of the spinal column, poor image quality, and absence of DTI. Nine patients were excluded owing to the absence of DTI, and 1 for partially missing data. Age, sex, chronicity of diabetes diagnosis (in years), HbA1c nearest to time of MRN, peak HbA1c, previous noncontributory MRIs (lumbar spine, pelvis, lower extremity), presenting symptoms (motor, sensory, pain), electrophysiology procedure data and impression, and field strength of MRN were recorded.

The anatomical MRN findings of nerve thickening, signal intensity alterations, and muscle denervation changes were originally recorded by one of two readers (board-certified, fellowship-trained musculoskeletal radiologists) as a standard of care. Findings were recorded on a Excel spread sheet by a medical student, then reviewed for accuracy by two board-certified, fellowship-trained musculoskeletal radiologists in consensus. Abnormal nerve findings from the original reports of the LS plexus nerve roots and peripheral nerves were recorded. Regional muscle denervation findings were also recorded. This was followed by formal bilateral DTI assessment blinded to the anatomical findings, which was the focus of this study.

Magnetic resonance image acquisition

The MRN of LS plexuses were performed on high-field scanners (1.5-Tesla and 3-Tesla magnets). The DTI protocol parameters included (repetition time 7,700–10,200 ms, echo time 64–80 ms, slice thickness 5 mm, interslice gap 0 mm, diffusion moments 0,600 s/mm^2, directions of interrogation 12, matrix 128 × 128. Axial DTIs were obtained from L3 vertebra to lesser trochanter levels. A combination of a large torso coil and posterior spine coil elements was used for imaging. The axial DTIs were matched to anatomical images—axial T1-weighted and axial fat-suppressed T2-weighted imaging—for localization purposes during image evaluation.

Data collection

All studies were assessed by a primary reader (reader 1, medical student and a board-certified, fellowship-trained musculoskeletal radiologist in consensus) for a total of 848 measurements (16 per study × 53 studies). Thirty percent of all studies and measurements were randomly and independently assessed by a secondary reader (reader 2, board-certified, fellowship-trained musculoskeletal radiologist) to evaluate the inter-rater reliability. A training session with five scans between the readers was completed before making independent measurements. Freehand regions of interest (ROIs) were drawn around bilateral L3, L4, L5, S1, S2, femoral, and sciatic nerves, in addition to bilateral iliacus muscles on B600s. LS nerve roots were measured at the juxta-foraminal location (Figs. 1, 2). The femoral nerves were measured at the level of the exiting L5 nerve root in the iliopsoas triangle (Fig. 3a), whereas the sciatic nerves were measured at two locations: the ischial spine and the tuberosity (Fig. 3b, c respectively). The perineural fat of all nerves was carefully excluded to include only the nerve itself. The DICOM DTI data were post-processed using independent software (Intellispace portal 8.0; Philips, Best, Netherlands) to calculate the minimum and mean signal intensity from the b = 600 maps, ADC, and FA from the scans. The image quality of the examination was assessed by a board-certified, fellowship-trained musculoskeletal radiologist as per the following categories: motion (0 absent, 1 mild, 2 moderate, 3 severe, 4 nondiagnostic), fat suppression (0 poor, 1 sub-optimal, 2 good, 3 excellent), and overall image quality (0 poor, 1 sub-optimal, 2 satisfactory, 3 good, 4 excellent). All images were diagnostic with good to excellent quality; no exclusions were made based on the above criteria.

Statistical analysis

Qualitative findings from MRN reads were recorded with descriptive statistics. Quantitative findings were assessed using a factorial ANOVA with IBM SPSS statistics version 23 to compare the diffusion parameters of cases versus controls while controlling for nerve location. A multiple linear regression analysis was performed to determine the relationship between nerve diffusion value (minimum and mean values of B600, ADC, and FA) and HbA1c (at the time of the study) while controlling for the following variables: age, sex, BMI, and nerve location. An intraclass correlation coefficient was performed to assess agreement between readers. Pearson Chi-squared

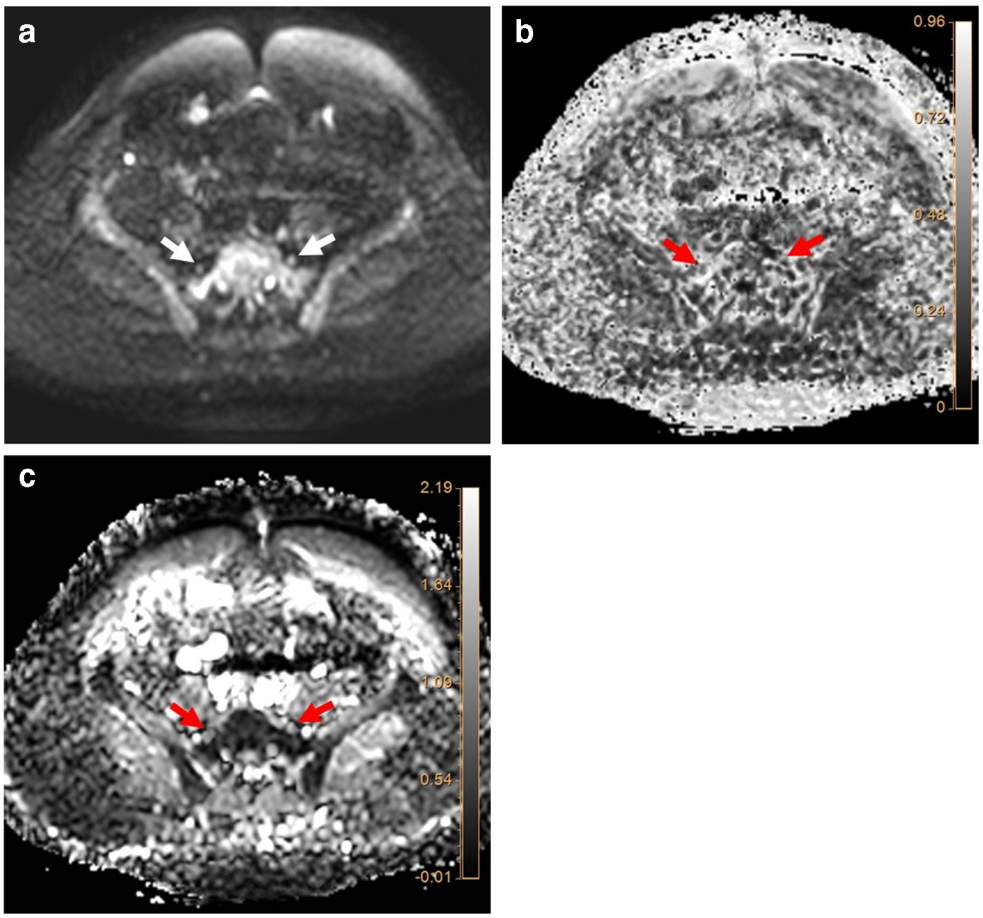

Fig. 1 Diffusion tensor imaging of a control patient. Axial slice of the L5 nerve roots (*white and red arrows*) in a control patient on **a** B600, **b** fractional anisotropy, and **c** apparent diffusion coefficient as they exit the neural foramen. The minimum B600 signal intensity of the right and left L5 nerve root were 83.56 and 106.77 respectively; the mean B600 signal intensities were 194.04 and 265.2 respectively. The minimum apparent diffusion coefficients (ADCs) of the right and left L5 nerve roots were 1.20e-4 and 1.00e-4 respectively; the mean ADCs were 1.15e-3 and 1.15e-3 respectively. The minimum fractional anisotropies (FAs) of the right and left L5 nerve roots were 0.38 and 0.29 respectively; the mean FAs were 0.58 and 0.62 respectively

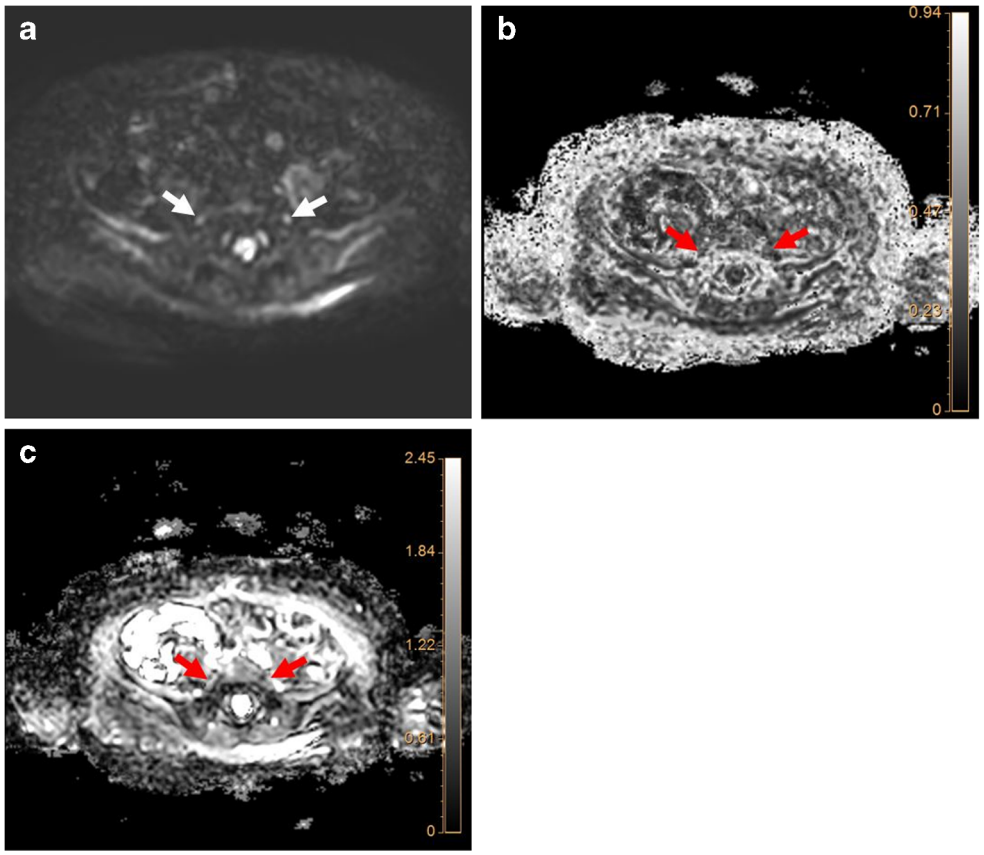

Fig. 2 Diffusion tensor imaging of a diabetic amyotrophy (DA) case patient. Axial slice of the L5 nerve roots (*white and red arrows*) in a case patient on **a** B600, **b** FA, and **c** ADC as they exit the neural foramen. The minimum B600 signal intensities of the right and left L5 nerve root were 93.50 and 91.32 respectively; the mean B600 signal intensities were 194.48 and 151.84 respectively. The minimum ADCs of the right and left L5 nerve roots were 1.3e-3 and 5.20e-4 respectively; the mean ADCs were 1.80e-3 and 1.62e-3 respectively. The minimum FAs of the right and left L5 nerve roots were 0.21 and 0.18 respectively; the mean FAs were 0.39 and 0.48 respectively

tests were performed on categorical demographic variables and independent samples *t* tests were performed on continuous demographic variables. A receiver operating characteristic curve analysis was performed for minimum and mean ADC and FA values.

Results

Control and case demographics

Demographic variables are shown in Table 1. In the control group, there were 20 males and 20 females. The average patient age was 61.25 ± 12.00 years. The average patient BMI was 25.82 ± 4.33. In the case group, there were 7 males and 6 females. The average patient age was 62 ± 16.06 years. The average patient's BMI was 26.52 ± 4.91. Patients within the DA case group were not significantly different from the control group in terms of age, sex, or BMI. In the control group, 2 out of 40 scans were acquired on 1.5-T machines. In the case group, 5 out of 13 scans were acquired on 1.5-T machines. Because of the small numbers, we did not perform statistical analysis, although it was suspected that the heterogeneity of the scanner strength did not have a substantial impact on the qualitative nerve assessment.

Clinical history

All clinical findings are shown in Table 2. The average length of diabetes diagnosis was 15.46 ± 9.56 years. The average HbA1c at the time of the study was 6.86 ± 1.42. The average highest recorded HbA1c was 8.98 ± 1.42. The presenting symptoms of the patients were pain ($n = 9$), motor weakness ($n = 10$), and altered sensation ($n = 8$).

Previous clinical diagnostic testing

Electrophysiology was performed in 11 out of 13 patients in this study. The results were diagnostic of DA ($n = 1$ patient), equivocal with other multiple differentials, such as radiculopathy, peripheral motor-sensory neuropathy, etc. ($n = 9$), and unremarkable ($n = 1$). Several patients had previously undergone noncontributory pelvic MRI ($n = 3$), knee MRI ($n = 0$), or lumbar spine MRI ($n = 10$) studies.

MRN findings

The anatomical nerve findings of abnormal thickening and/or hyperintensity were recorded and confirmed in the LS plexus nerve roots ($n = 11$ patients), sciatic nerves ($n = 10$), femoral nerves ($n = 13$), and obturator nerves

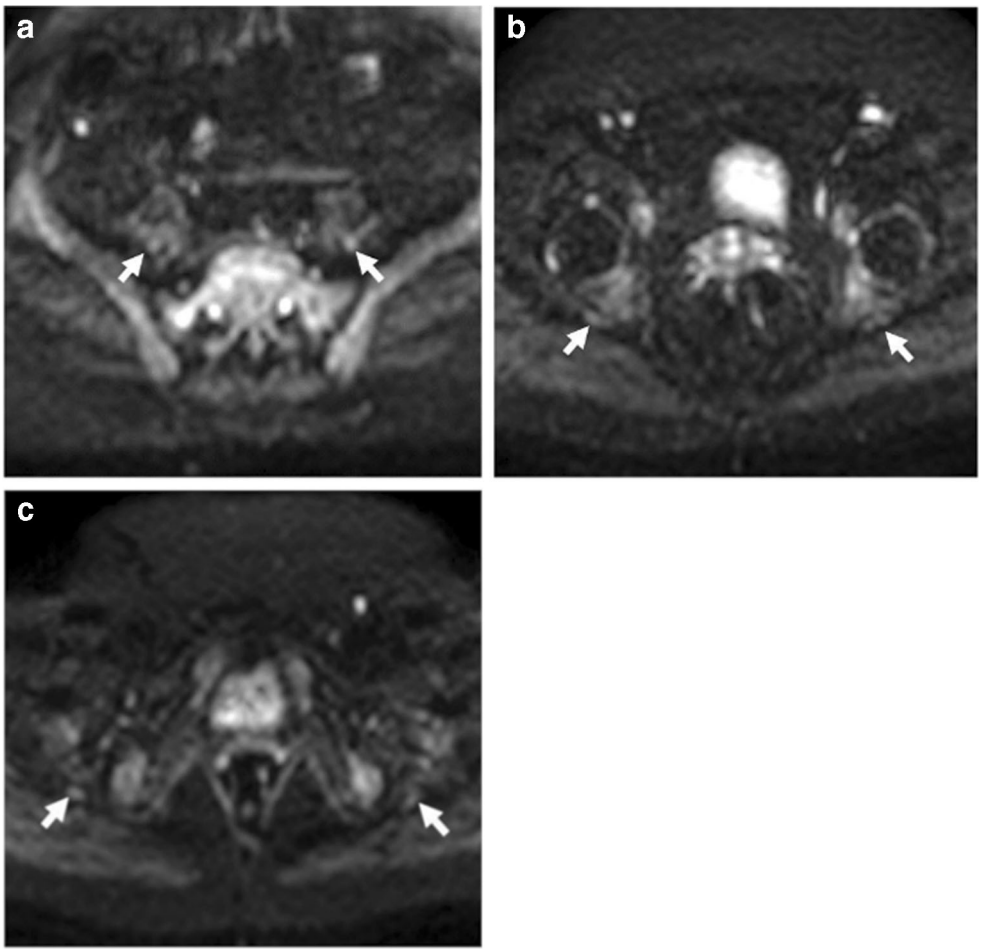

Fig. 3 Femoral and sciatic measurement locations in a control patient. Locations (*white arrows*) at which **a** the femoral and **b**, **c** sciatic nerves were measured on B600. The femoral nerve was measured at the level of the L5 nerve root in the iliopsoas triangle. The sciatic nerve was measured proximally and distally, at the level of the ischial spine and tuberosity respectively

($n = 4$). An example may be seen in Fig. 4a. The muscle findings of denervation (diffuse edema-like signal and/or atrophy without fascial edema) were recorded and confirmed in the psoas muscles ($n = 4$ patients), piriformis ($n = 6$), gluteal ($n = 9$), hamstrings ($n = 3$), proximal quadriceps ($n = 4$), adductors ($n = 6$), iliacus ($n = 0$), quadratus femoris ($n = 1$), or para-spinal muscles ($n = 6$) respectively. An example may be seen in Fig. 4b.

Quantitative nerve findings

The minimum nerve signal on B600 was significantly lower in the diabetic nerves than in controls ($F = 51.920$ [1830]; $p < 0.001$). Mean nerve signal on B600 was significantly lower in diabetic nerves than in controls ($F = 102.620$ [1830]; $p < 0.001$; Figs. 1a, 2a). The minimum nerve ADC value was significantly greater in diabetic nerves than in controls ($F = 24.756$ [1830]; $p < 0.001$). The mean nerve ADC value was significantly greater in diabetic nerves than in controls ($F = 9.513$ [1830]; $p = 0.002$; Figs. 1b, 2b). The minimum nerve FA value was not significantly different in diabetic nerves than in controls ($F = 1.853$ [1798]; $p = 0.174$). The mean nerve FA value was significantly lower in diabetic nerves than in controls ($F = 4.172$ [1798]; $p = 0.041$; Figs. 1c, 2c, Table 2). Nerve signal on B600, ADC values, and FA values all varied significantly with nerve location. However, there was no significant interaction effect between the presence of DA and nerve location on diffusion signal/value (Table 3).

Table 1 Patient demographics: controls and cases

	Controls ($n = 40$ patients)	Cases ($n = 13$ patients)	p value*
Age (years)	61.25 ± 12.00	62 ± 16.06	0.858
Sex (male, female)	20, 20	7, 6	0.814
BMI	25.82 ± 4.33	26.52 ± 4.91	0.630

*Independent t and Chi-squared tests were used for continuous and categorical variables respectively

Table 2 Clinical data and qualitative nerve findings on magnetic resonance neurography (MRN)

Parameter	Values	
Length of diabetes diagnosis (years), mean, SD	15.46	9.56
HbA1c at the time of study, mean, SD	6.86	1.42
Highest recorded HbA1c, mean, SD	8.98	1.42
Presenting symptoms, *n*, %[a]		
Pain	9	69.23
Motor	10	76.92
Sensory	8	61.54
Previous nondiagnostic MRIs, *n*, %		
MRI lumbar spine	10	76.92
MRI pelvis	3	23.08
MRI knee	0	0
Electrophysiology studies, *n*, %		
Diagnostic of diabetic amyotrophy	1	7.69
Equivocal	9	69.23
Unremarkable	1	7.69
Nerve findings		
Lumbosacral plexus	11	84.62
Sciatic nerves	10	76.92
Femoral nerves	13	100
Obturator nerves	4	30.77
Muscle findings, *n*, %		
Psoas major	4	30.77
Piriformis	6	46.15
Gluteal	9	69.23
Hamstrings	3	23.08
Proximal quadriceps	4	30.80
Adductors	6	46.15
Iliacus	0	0
Quadratus femoris	1	7.69
Para-spinal	6	46.15

HbA1c hemoglobin A1c

[a] Percentage is defined as the count divided by the sample size ($n = 13$)

Correlation with HbA1c

Minimum and mean ADC correlated positively with highest recorded HbA1c ($\beta = 0.518$, $p < 0.001$ and $\beta = 0.302$, $p = 0.020$ respectively) while controlling for sex, age, and BMI. Minimum FA, mean FA, minimum B600, and mean B600 did not significantly correlate with highest recorded HbA1c. The area under the curve calculated from the receiver operator characteristic curve analysis was 0.601, 0.569, 0.468, and 0.471 for minimum ADC, mean ADC, minimum FA, and mean FA respectively (Figs. 5, 6).

Inter-rater analysis

Intraclass coefficients between readers were 0.892 ($p < 0.001$, 95% confidence interval [CI]: 0.866–0.914) for B600 values, 0.717 ($p < 0.001$, 95% CI: 0.675–0.754) for ADC values, and 0.730 ($p < 0.001$, 95% CI: 0.689–0.766) for FA values.

Discussion

In this case–control analysis of DA nerves, we found that minimum B600 signal, mean B600 signal, and mean FA values were significantly lower in DA cases than in controls, whereas minimum and mean ADC values were significantly higher in DA cases than in controls. Although the B600 findings were unexpected, the ADC and FA findings are analogous to those from previous studies of diabetic peripheral neuropathies [18, 19]. The significantly lower B600 signal in DA cases may be due to a combination of fatty change in the nerve and intraneural edema [13].

The observed increase in ADC and decrease in FA values are expected outcomes of demyelinated and/or degenerated nerves [16]. Changes seen in DA are believed to be secondary to inflammation. Nerve biopsies from DA patients have been shown to exhibit higher levels of several markers of

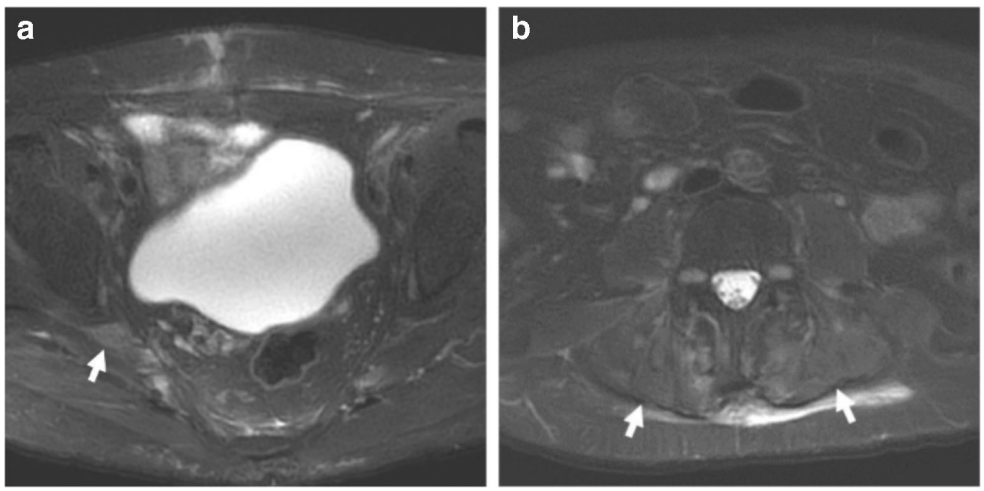

Fig. 4 Nerve and muscle findings on MRN of a DA case patient. **a** Nerve and **b** muscle findings of a patient with DA (*white arrows*) on a T2-weighted fat-suppressed image. The patient is an 81-year-old woman presenting with right-sided pain, weakness, and sensory loss. The patient's right sciatic nerve exhibits marked thickening and abnormal signal and the para-spinal muscles exhibit patchy edema-like signal

Table 3 Estimated marginal means of diffusion tensor imaging values for controls and cases

	Controls	Cases
Minimum B600	71.73 (95% CI: 67.32 to 76.14)	39.06 (95% CI: 67.32 to 76.14)
Mean B600	172.64 (95% CI: 163.81 to 181.47)	80.75 (95% CI: 65.29 to 96.21)
Minimum ADC	7.36e-4 (95% CI: 7.04e-4 to 7.68e-4)	8.99e-4 (95% CI: 8.43e-4 to 9.56e-4)
Mean ADC	1.50e-3 (95% CI: 1.48e-3 to 1.52e-3)	1.56e-3 (95% CI: 1.53e-3 to 1.59e-3)
Minimum FA	0.232 (95% CI: 0.225 to 0.239)	0.221 (95% CI: 0.208 to 0.235)
Mean FA	0.451 (95% CI: 0.444 to 0.458)	0.435 (95% CI: 0.422 to 0.448)

CI confidence interval, *ADC* apparent diffusion coefficient, *FA* fractional anisotropy

inflammation, namely NF-κB, TNF-alpha, and ICAM1 [6]. Moreover, immunotherapy is currently being studied as a therapeutic method in these patients [20–22]. These inflammatory changes are likely to be picked up by DTI [16]. The diffusion properties of water along an axon are altered when nerve architecture is disrupted by inflammatory change, and this is displayed by decreased FA and increased ADC.

To our knowledge, this is the first study to characterize the nerves and muscles of patients with confirmed DA using DTI, and to attempt quantitation of DA nerve lesions. It should be noted that all DA cases also exhibited abnormalities of multiple nerves and regional muscles on the T2-weighted fat-suppressed anatomical MRN images. Although there may be a value in the follow-up of such cases quantitatively using this advanced imaging, currently, the diagnosis can be accomplished using anatomical MRN. We did not quantify T2 signal, as that does not mirror the current practice and is a subject for future research.

Clinical findings demonstrated that electrophysiology was confirmatory in only 1 out of 11 DA cases in which such studies were employed. Clinically, MRN was more successful in confirming DA than electrophysiology. It is, however, possible that patients for whom MRN was ordered had more challenging diagnoses. MRN provides several advantages over electrophysiology. Electrophysiology studies are known to be invasive tests, which may be uncomfortable for patients [10]. The accuracy of the results may suffer from practical limitations (pH, temperature, body habitus), and may not sufficiently detect deep nerve architecture [7–9]. Electrophysiology studies do not directly visualize nerves, but instead rely on indirect signs of nerve damage and may not differentiate a focal lesion from a diffuse process. Furthermore, electrophysiology is often negative until the disease has progressed to a measurable degree [23, 24]. As a side note, other MRI studies ordered before the initial MRN were noncontributory in most of the

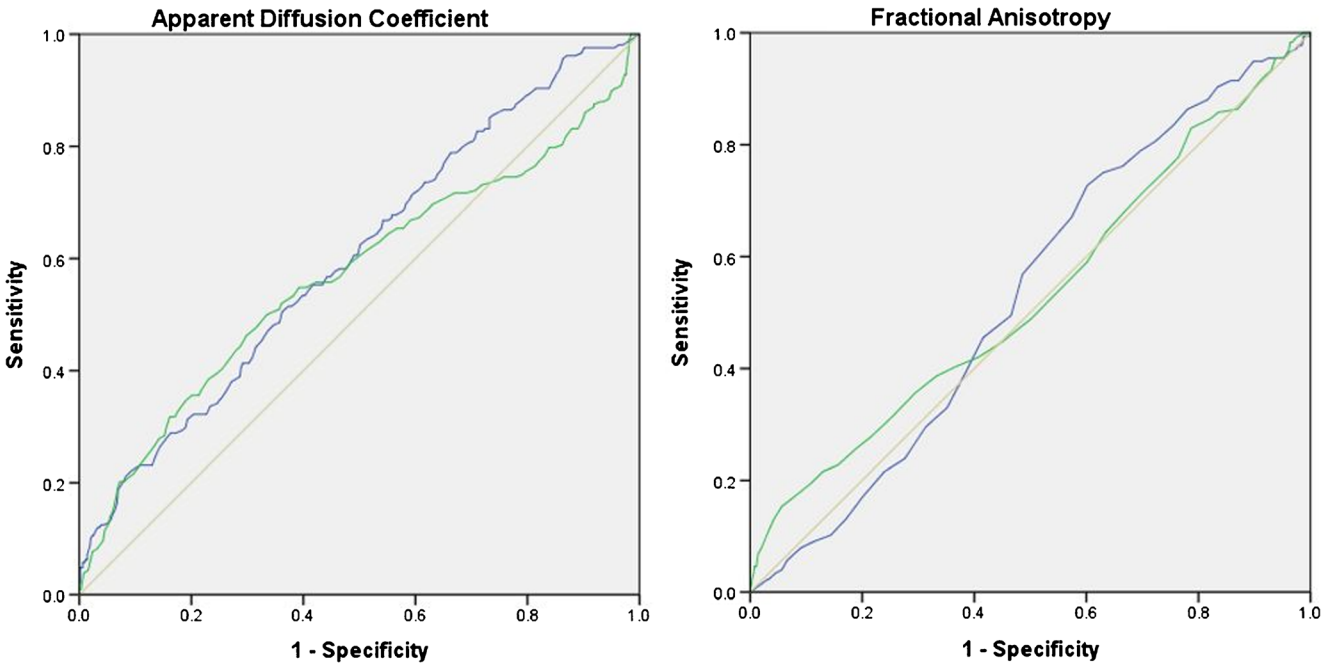

Fig. 5 Receiver operating characteristic (ROC) curves. The ROC curves for **a** ADC and **b** fractional anisotropy. The *blue line* denotes minimum values, the *green line* denotes mean values, and the *grey line denotes the reference line*

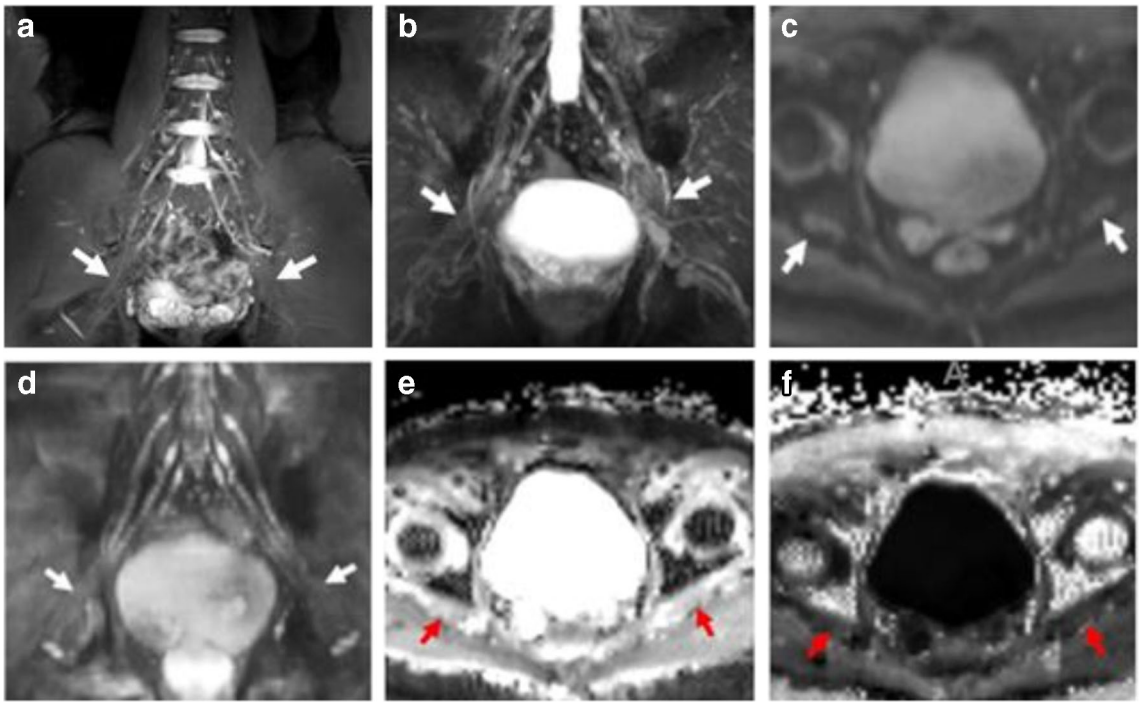

Fig. 6 Maximum intensity projections on MRN of a control and a DA case: sciatic nerves. **a** The maximum intensity projection of a 3D T2-weighted fat-suppressed (T2FS) image in the coronal plane of a control. **b** The maximum intensity projection of a T2FS image in the coronal plane is shown for a DA case patient. The DA case patient is a 60-year-old man who presented with bilateral lower extremity pain, weakness, and paresthesia, and was subsequently diagnosed with DA. Bilateral sciatic nerves (*red and white arrows*) are increased in signal and size with a more pronounced pathological condition on the right-hand side. The **c** B600, **d** B600 maximum intensity projection, **e** ADC, and **f** FA are shown

patients, highlighting the need for a more sensitive imaging modality.

Interestingly, patients with DA can have HbA1c levels that are only mildly elevated. Previous studies have presented similar findings [4, 23]. However, HbA1c was significantly related to minimum and mean ADCs in the expected directions. For the first time, subtle changes in DA nerve architecture with variation in HbA1c are revealed.

This study has many limitations. The patient population in this study is relatively small and was observed retrospectively because of the uncommonly encountered entity of DA. Another limitation was that nerve diffusion values vary along the length of any given nerve in the LS plexus, and the scans were obtained on both 1.5-T and 3-T scanners with similar protocols [25]. As it is impossible to standardize these measurements, some variation in the results may be attributed to this phenomenon. However, this limitation affects measurements in DA cases and controls, and because measurements were made at fixed locations in all studies in a standardized manner, it should not greatly affect differences observed between the groups. Finally, there could be differences due to different magnet strengths, but the numbers were too small to determine any meaningful differences using statistical tests. Although 3-T imaging improves the resolution of MRN, it is unlikely that it has much of an impact on the qualitative assessment of brightness and thickness, and such results can be used in practice while making the diagnosis of nerve pathology.

In conclusion, neuromuscular lesions secondary to DA are quantitatively identified on DTI with moderate accuracy, and positive correlation of ADC levels with serum HbA1c levels exists. Thus, MRN with DTI can be employed as a non-invasive diagnostic tool in patients when there DA is suspected. Further studies should assess a larger cohort of patients with or without follow-up scans when regulating and controlling HbA1c.

Compliance and ethical standards

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. Institutional Review Board approval was obtained and informed consent was waived.

Conflicts of interests The authors declare that they have no conflicts of interest. Avneesh Chhabra declares relationships with the following companies: consultant for ICON Medical and Treace Medical Inc. and receives royalties from Jaypee and Wolters. None of the other authors has any relationships to declare.

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