Diffusion tensor imaging of the median nerve healing.
Preliminary results

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AIMS: *This study aimed to examine the correlation between DTI, clinical assessment, and electromyography results in patients who underwent primary median nerve repair.*
METHODS: *Ten patients who underwent primary repair of the complete median nerve transection were included. Study assessments were performed on both the traumatized and non-traumatized extremities and patients were followed up for a minimum duration of 11 months. Clinical assessments, (Tinnel test, static 2-point discrimination test, motor and quality of life assessments), electromyography and DTI were performed.*
RESULTS: *None of the clinical or electromyographic parameters correlated significantly with any of the diffusion tensor imaging parameters, i.e. fractional anisotropy (FA) or apparent diffusion coefficient (ADC) ($p>0.05$ for all). In addition, The Disabilities of the Arm, Shoulder and Hand (DASH) scores did not correlate with either FA ($r=0.55$, $p=0.098$) or ADC ($r=0.40$, $p=0.260$) values. However, Tinnel positive cases ($n=3$) had lower relative FA when compared to Tinnel negative cases ($n=7$) (-0.11 ± 0.19 vs. 0.05 ± 0.04, $p=0.033$).*
CONCLUSION: *Our findings do not support the presence of relations between DTI parameters and electromyographic or most of the clinical parameters. Further MRI studies with larger numbers of patients with complete transection of the median nerve using the novel imaging parameters are warranted.*

KEY WORDS: Diffusion Tensor Imaging (DTI), Electromyography (EMG), Median nerve, Nerve injury, Nerve repair

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Ethical approval
The study protocol was approved by local ethics committee (approval date January 23, 2015; no. 2015/59).
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Introduction

The median nerve is one of the three major nerves of the forearm and courses under the superficial flexor tendons and the flexor retinaculum at the wrist level, where most of the traumatic injuries occur. Despite advances in the field of microsurgery, which is the standard treatment modality for traumatic median nerve injuries, complete functional improvement is rarely achieved, particularly with regard to motor functions.[1]
Until now, a variety of methods have been utilized to assess the degree of nerve regeneration following surgical repair. Clinical examinations and nerve conduction studies with EMG are frequently employed for monitoring the rate of improvement. Nerve conduction

studies assess the velocity and strength of an electrical impulse conducted through the course of a peripheral nerve. However, novel methods for monitoring the success of treatment are warranted, as both clinical tests and EMG are in fact subjective assessments that require the involvement of an experienced neurologists.

Diffusion tensor imaging (DTI) sequence is a magnetic resonance imaging (MRI) modality which allows visualization of the orientation of axonal structures. Also DTI is one of the imaging techniques used for the early diagnosis of certain neurodegenerative disorders of the central nervous system (e.g. Parkinsonism) with normal appearance on conventional [2]. DTI of peripheral nerves was first described in 2004 [3]. The identified differential diffusion characteristics of intact, healing, or injured nervous tissues have suggested that the healing of nervous tissues may be monitored using DTI.

The aim of the study was to investigate the correlation between DTI, clinical assessment, and electromyography results in patients who was exposed primary repair following total median nerve transection.

Methods

Patients

A total of 10 patients who was exposed primary repair of the complete median nerve transection after admission to the emergency unit of our institution between May 2014 and March 2015 were included in this study. Patients were followed up for a minimum duration of 11 months. Study assessments were performed on both the traumatized and non-traumatized extremities.

Clinical Assessments

Tinnel test and static 2-point discrimination test (s-2PD[4] were used for sensory assessments. Presence of electrical sensations (tingling) distal to the repair site upon percussion was considered Tinnel test positivity (also the same test was applied at the same position on the normal site), while those without such sensations were considered Tinnel test negative. The static 2-point discrimination ability was calculated in millimeters.

Motor assessments were based on the opposition strength of the first finger and graded according to British Medical Research Council (MRC) scale[5]

The life quality and patient satisfaction after nerve repair were assessed using DASH (The Disabilities of the Arm, Shoulder and Hand) scoring system [6], which consists of 30 main items as well as 8 additional items for evaluating occupational effects. Higher scores reflect lower quality of life and satisfaction.

Electromyography

For electrodiagnostic assessments, the AANEM (American Association of Neuromuscular and Electrodiagnostic Medicine) guidelines for carpal tunnel syndrome was used. All EMG examinations were performed using a Medelec Synergy device (Oxford Instruments Medical, Surrey, UK). The skin temperature was measured with a digital thermometer and maintained over 32 °C during the procedure. In both intact and injury sites, the nerve conduction velocity and amplitude of the median nerve as well as the motor conduction velocity and distal motor latency were measured. Also,

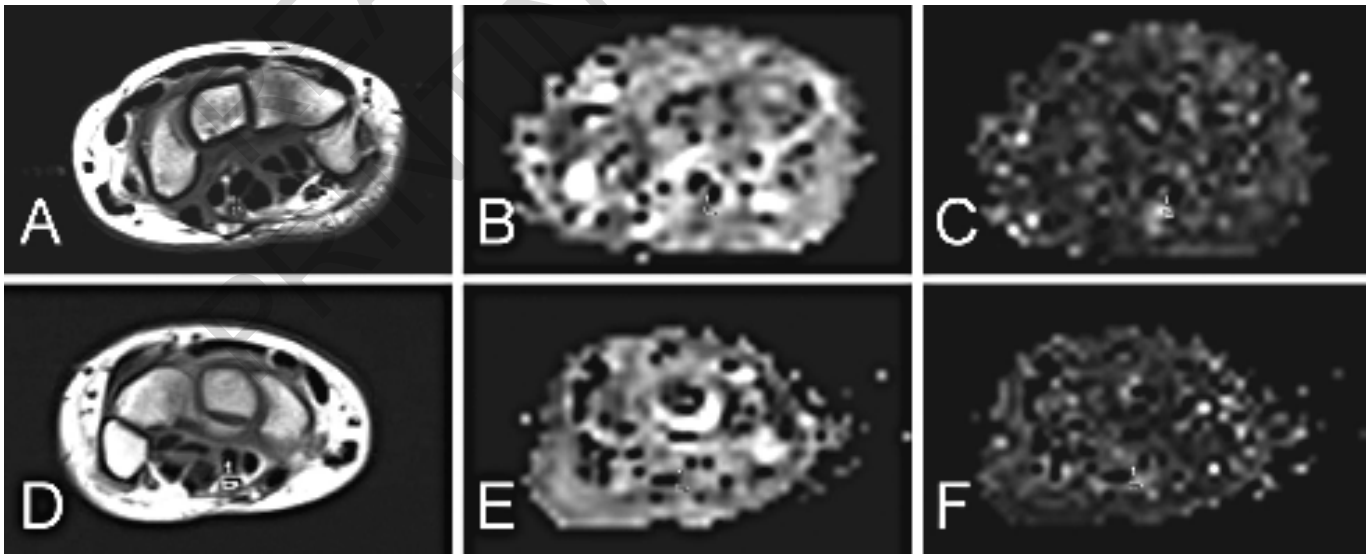

Fig. 1: Right (lacerated, A; B; C) and left (normal, D; E; F) wrists of an 18-year-old female. T1-weighted spinechoaxial MR image (A) at the level of the pisiform bone shows right median nerve (region of interest-ROI). Corresponding ADC (B) and FA (C) maps show ROI placements to obtain mean ADC and FA values. Left wrist of same patient is evaluated using the similar method. Left median nerve and ADC and FA value measurements are demonstrated on T1-weighted spinecho axial MR image (D), corresponding ADC (E) and FA (F) maps.

compound muscular action potential (CMAP) amplitude was measured in the muscle, in which the motor nerve was stimulated. During motor conduction tests, stimulation was performed at the wrist and forearm, with recording at the thenar eminence. For sensory conduction tests, stimulation was performed at the wrist level with recording performed at the second finger using ring electrode.

Diffusion Tensor Imaging

The MR protocol used for the study included routine MR imaging of the wrist using the 16-channel wrist coil with T1- and T2-weighted and fluid attenuated inversion recovery (FLAIR) sequences in addition to DTG sequences. Accordingly, the following DTI sequence parameters were used: axial, TR=3900 ms, TE = 79 ms, number of cross sections = 22, FOV =120x120 mm, Matrix: 64×64, cross-sectional thickness = 4 mm, NSA=2 (b=0) and 6 (b=1000), b=0 - 1000 s/mm^2 and 12 diffusion direction. MR images were post-processed by using Syngo MR D13 Numaris/4 software (Siemens Medical Solutions, Erlangen, Germany). T1-weighted turbo spin echo sequence was used for anatomical correlation. The median nerve was first identified at the level of the pisiform bone. Then, freehand region of interest (ROI) was positioned on the cross-sectional area of the median nerve on the axial T1-weighted turbo spin echo image. ROIs were drawn smaller than the nerve to avoid partial volume effects. Matched ROIs were placed synchronously on the FA and ADC maps by software. Mean FA and ADC values were calculated automatically on the corresponding FA and ADC maps. In all patients, continuity of the nerve was demonstrated using tractography (Fig. 1).

Statistical Analysis

Statistical Package for Social Sciences (SPSS) version 21 was used for statistical analysis. Normality was tested using Shapiro-Wilk test and graphical methods. Correlations between continuous variables were tested using Spearman's test. For each variable, the difference between injured side minus intact side was used for correlation analyses. Mann-Whitney-U test was used to test FA and ADC differences in Tinnel positive versus negative groups. A p value <0.05 was considered an indication of statistical significance.

Results

Patients mean age was 26.8±7.3. Nine patients were male (90%) one was female (10%). The injury was on the right side in 6 cases (60%) and on the left side in 4 cases (40%). The mean DASH score was 5.5±3.6.

Table I - *Correlations between diffusion tensor imaging findings versus clinical and electromyographic parameters*

	FA	ADC
Clinical tests		
2-point discrimination, mm	r=-0.50, p=0.141	r=-0.35, p=0.319
Motor assessment score	r=0.16, p=0.668	r=0.39, p=0.266
Electromyography findings		
Sensory velocity, m/sec	r=0.48, p=0.233	r=0.38, p=0.352
Sensory amplitude, μV	r=-0.10, p=0.823	r=0.05, p=0.911
Motor velocity, m/sec	r=-0.25, p=0.516	r=0.00, p=1.000
Motor latency, msec	r=-0.30, p=0.433	r=0.03, p=0.932
Compound muscle action potential, mV	r=-0.17, p=0.668	r=0.22, p=0.576

For the continuous variables above, the difference between injured side minus intact side was used for analyses. FA, fractional anisotropy; ADC, apparent diffusion coefficient.

Table I shows correlation analysis between radiological versus clinical/electromyographic parameters. None of the clinical or electromyographic parameters correlated significantly with any of the diffusion tensor imaging parameters (p>0.05 for all). In addition, DASH score did not correlate with either FA (r=0.55, p=0.098) or ADC (r=0.40, p=0.260) values. However, Tinnel positive cases (n=3) had lower relative FA when compared to Tinnel negative cases (n=7) (-0.11±0.19 vs. 0.05±0.04, p=0.033). On the other hand, Tinnel positive and negative cases did not differ with respect to ADC values (0.08±0.30 vs. 0.14±0.16, p=0.833).

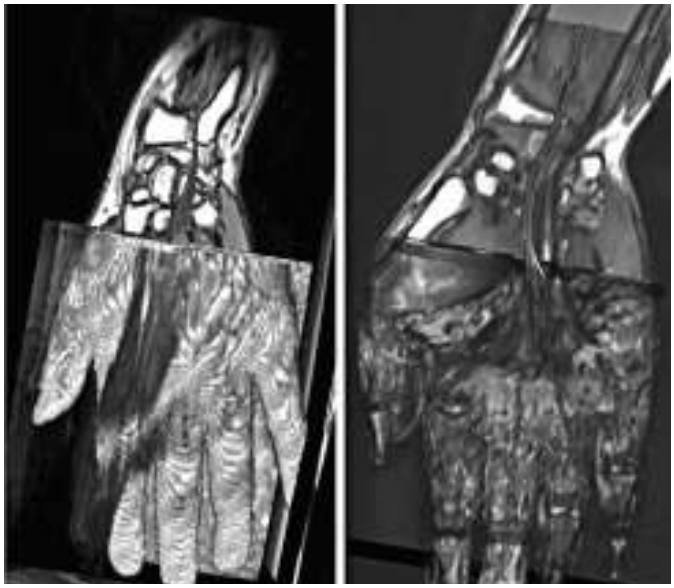

Fig. 2 Tractography images of the same 18-year-old female patient showing the median nerve in blue color. Right, injured extremity; left normal extremity.

Discussion

Accurate documentation and quantification of peripheral nerve axonal changes are critically important for clinical research in peripheral nerve disorders such as nerve trauma or peripheral neuropathy. On the other hand, such as electromyography (EMG) and nerve conduction studies are the current methods used for this purpose suffer certain limitations in these settings. For instance, studies have been found to provide a diagnostic accuracy of 85-90% in patients with carpal tunnel syndrome, with a false-negative rate of 10-15% in current [7]. In compresion syndromes, a diagnosis may be readily established when clinical symptoms and electrophysiology are clear. On the other hand, diversities in different measured clinical parameters may also lead to diagnostic controversies in many cases.

Because of the above-mentioned limitations of clinical and neurophysiological measurement methods, novel approaches to detect and quantify peripheral nerve degeneration and regeneration are needed to provide practical tools in the management of peripheral nerve disorders as well as more powerful instruments in clinical trials of novel therapeutic approaches. In this regard, diffusion tensor imaging (DTI), a magnetic resonance based technique, provides image contrast for nerve tracts and can be applied serially on the same subject with potential to monitor nerve fiber conten[88]. Existing techniques, i.e. electrodiagnostic and conventional imaging modalities, ensure important information; however, they have limited ability to differentiate severe nerve [9].

Diffusion tensor imaging (DTI) of peripheral nerves on the other hand assesses the entirety of the nerve fibers at injury site; thus, represents a potential novel technique to localize and evaluate nerve injury. These two methods also hold promise as markers of early nerve regeneration, prior to clinical and electrodiagnostic evidence of recovery.

In this study, we aimed to investigate the correlation between electromyography and diffusion tensor imaging findings in patients who underwent surgical repair of the complete median nerve transection. To our knowledge, no previous studies have compared electromyography and diffusion tensor imaging results in a group of patients surgically treated for complete transection of the median nerve, although studies in animal models of complete transection [8] have been performed and the utility of DTI in the assessment patients with carpal tunnel syndrome have been examined previously [10].

In this study, we have not been able to demonstrate any correlations between clinical/electromyographic findings and diffusion tensor imaging parameters in patients who underwent surgical repair of complete median nerve transection. Also, no correlations between FA or ADC and quality of life scores could be identified. The only difference was between Tinel sign positive and negative patients in terms of FA values. Despite differences in study populations (i.e. complete transection vs. carpal tunnel syndrome) our observations seem partly at odds with previous findings reporting significantly lower fractional anisotropy values in carpal tunnel patients as compared to normal subjects [10] and another study reporting significant FA, radial diffusivity, and ADC differences between carpal tunnel patients and controls [11].

Also, in a mice model, FA was found to be the most sensitive measure in distinguishing between normal uninjured, transected, and regenerating nerves among other parameters [8]. These findings suggest that FA and ADC may not necessarily show a standard increase or decrease at the site of injury, which may possibly be explained by var [12]. Such structural variations may represent an obstacle for the standardization of FA and ADC values.

A major limitation of our study was the inclusion of only 10 patients with median nerve dissection. This may have obviously precluded statistically significant conclusions. Also, there are some important caveats to performing and interpreting peripheral nerve DTI, such as the need for balancing satisfactory image resolution and scan time during image acquisition [13]. Furthermore, reproducibility of peripheral nerve DTI parameters is also a prerequisite before using this technique as a surrogate marker of axonal injury. Also, data on the normative diffusion values of the median nerve such as FA and ADC are very scarce [14].

Nevertheless, the ability of DTI to visualize and characterize the median nerve in healthy subjects and carpal tunnel syndrome patients has been shown, and the need for objective and noninvasive diagnostic measures of axonal regeneration in peripheral nerves is increasingly realized. Conventional techniques such as EMG will not be able to detect nerve regeneration before nerve fibers have reached the target muscle, and this process may require months of monitoring, particularly in proximal nerve injuries.

In conclusion, further MRI studies with larger numbers of patients with complete transection of the median nerve using the novel imaging parameters are certainly warranted for immediate clinical and preclinical applications.

Riassunto

INTRODUZIONE: L'esame clinico e gli studi di conduzione nervosa con EMG sono spesso utilizzati per monitorare la velocità di recupero dopo la riparazione chirurgica di lesione neurale. Le caratteristiche di diffusione differenziale di tessuti nervosi intatti, in guarigione o danneggiati hanno suggerito che la guarigione dei tessuti nervosi può essere monitorata usando anche il DTI (imaging con tensore di diffusione).

OBIETTIVI: Lo scopo di questo studio è esaminare la correlazione tra DTI, valutazione clinica e i risultati dell'elettromiografia in pazienti che hanno subito la riparazione primaria del nervo mediano.

STUDIO: Studio di accuratezza diagnostica

METODI: Sono stati inclusi 10 pazienti sottoposti a riparazione primaria di completa sezione del nervo mediano. Le valutazioni dello studio sono state eseguite sia sulle estremità traumatizzate che sulle non traumatizzate e i pazienti sono stati seguiti con un follow up di almeno 11 mesi. Sono state effettuate valutazioni cliniche (Tinnel test, test di discriminazione di 2 punti statici, valutazione motoria e della qualità di vita), elettromiografia e DTI.
RISULTATI: Nessuno dei parametri clinici o elettromiografici ha dimostrato una correlazione statisticamente significativa con alcuno dei parametri dell'imaging con tensore di diffusione, i.e. anisotropia frazionale (FA) o coefficiente di diffusione apparente (ADC) (p>0.05 per tutti). In aggiunta, lo score DASH (Disabilities of the Arm, Shoulder and Hand) non ha dimostrato correlazioni con i valori di FA (r=0.55, p=0.098) o ADC (r=0.40, p=0.260). Tuttavia, i casi positivi al Tinnel test (n=3) hanno avuto una minor relativa FA rispetto ai casi negativi al Tinnel test (n=7) (-0.11±0.19 vs. 0.05±0.04, p=0.033).
CONCLUSIONI: I nostri risultati non supportano la presenza di correlazioni tra i parametri di DTI e parametri elettromiografici o la maggior parte dei parametri clinici. Sono necessari ulteriori studi di RMN con un maggior numero di pazienti con completa sezione del nervo mediano utilizzando i nuovi parametri di imaging.

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