Diffusion tensor imaging of forearm nerves for early diagnosis of multifocal motor neuropathy

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Audience: Clinicians and researchers interested in imaging nerves in peripheral nerve disorders

Background and purpose: Multifocal motor neuropathy (MMN), a peripheral neuropathy, is a rare immune-mediated disorder that affects 1-2 person per 100.000.[1] The disease is characterized by its progressive, multifocal, asymmetric distal limb weakness without any sensory involvement. Motor deficit usually starts in the hands and can spread to arms and feet.[2] Due to the progressive pure motor weakness, MMN is often confused with amyotrophic lateral sclerosis (ALS). However, unlike MMN, the symptoms of ALS are rapidly progressive and often affect the lower and upper motor neuron, whereas MMN only affects the lower motor neurons.[1] ALS is a fatal condition, the mean survival is three to five years after diagnosis[3], whereas MMN patients have a normal life expectancy. Nevertheless, due to progressive axonal loss in the demyelinated nerves, MMN patients can be long-term disabled.[1] Early detection of MMN and discriminating this disease from ALS is highly important as the start of immunoglobulin therapy prevents rapid degeneration of myelin in MMN. Current diagnosis in MMN include electromyogram (EMG) to indicate potential conduction blocks in MMN, discriminating it from ALS. However, in some cases conduction blocks cannot be identified although MMN is the underlying etiology.[2] Here, we test the feasibility of magnetic resonance imaging (MRI), diffusion tensor imaging (DTI) and fiber tractography (FT) to explore potential changes of diffusion values in the peripheral nerves in the forearm to distinguish MMN patients from ALS patients.

Methods: Local institutional review board approval was obtained for this study and written informed consent was given prior to the MRI examination. As part of an ongoing study, 8 MMN patients, 3 ALS patients, and 5 healthy controls underwent MRI for both forearms on a 3 Tesla MR system (Achieva; Philips Healthcare, Best, The Netherlands) using a 32-channel phased-array surface coil. DTI was performed based on diffusion-weighted spin echo single-shot echo planar imaging (EPI) in the axial plane with the following parameters; TE = 66 ms, TR = 6340 ms, SENSE factor 2, FOV 240 × 120 mm², matrix size 160 × 80, 60 slices with thickness = 4.0 mm, resulting in a voxel size of 1.5 × 1.5 × 4.0 mm³, half scan 0.69, SPIR fat suppression, b-values 0, 400 and 800 s/mm², and 15 gradient directions for each b-value. The total acquisition time was 9:32 minutes. As an anatomical reference, an axial T2 SPAIR, T1 TSE, and T2 TSE images were obtained. An EMG was obtained to identify conduction blocks. Scans with low SNR or high motion distortion were excluded, leaving 10 arms in MMN patients, 4 arms in ALS patients and 9 arms in healthy controls. DTI scans were corrected for motion distortion with the diffusion MRI-toolbox *ExploreDTI* and tensors were fitted using the REKINDLE procedure.[4] Whole volume tractography was used with a threshold of 0.30 on the FA index. SEED ROIs were placed at different levels of the nerves. The images with b-value 800 were used to calculate the fractional anisotropy (FA), mean diffusivity (MD), axial diffusivity (AD), and radial diffusivity (RD). A linear mixed model was used to compare nerves in the three groups. Correction for clustering was integrated in this model.

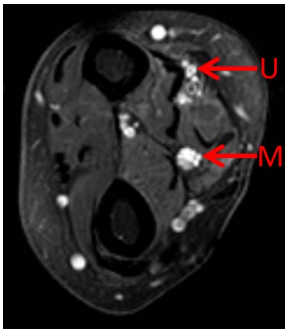

Figure 1: T2 SPAIR showing the median nerve (M) and the ulnar nerve (U)

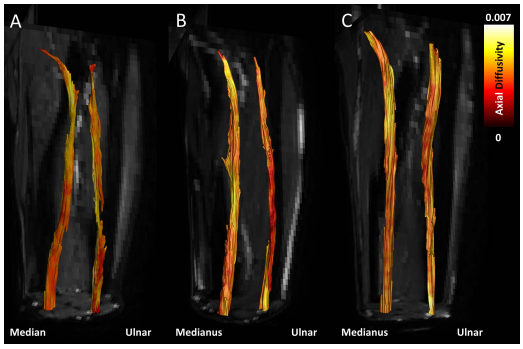

Figure 2: Axial diffusivity color map of the median and ulnar nerve in A) MMN patient, B) ALS patient, and C) healthy control. In some MMN patients it was not possible to track the entire nerve (see ulnar nerve in A).

Results: Nerve conduction studies confirmed conduction blocks in median or ulnar nerve in all MMN patients, which were not found in any of the included ALS patients nor healthy controls.
From the DTI images it was possible to reconstruct the median and ulnar nerves in the forearm in MMN, ALS and healthy controls using FT. On average, 5 SEED ROIs were needed to perform the tractography, where maximal 2 ROIs were needed to track the nerves in healthy controls and ALS patients. This could be related to the shorter tract length of the fibers during FT in MMN (mean fiber tract length: 78.3mm in MMN, 84.6mm in ALS, and 95mm in healthy controls). In some MMN cases it was not possible to find tracts along the entire nerve path and parts of the nerves in the FT results could not be identified although the nerves were clearly visible on the anatomical image (see figure 2A). In both ALS and healthy controls the nerves could easily be identified (see figure 2B, and 2C).
Comparisons between groups showed a significant difference ($p<0.05$) in FA and AD in MMN patients compared to healthy controls. No significant difference in FA and AD between MMN and ALS and between ALS and healthy controls was found.

Table 1 Diffusion parameters of MMN, ALS, and healthy controls (HC)

	Diffusivity (mm²/s) x 10^{-3}			
	FA	MD	AD	RD
MMN	0.44±0.02**	2.75±0.09	4.19±0.11**	2.03±0.10
ALS	0.46±0.03	2.74±0.07	4.30±0.18	1.93±0.14
HC	0.46±0.02**	2.82±0.09	4.42±0.12**	2.03±0.09

**MMN vs HC for FA and AD: $p<0.05$

Conclusion: This 3T MRI study shows the feasibility of DTI and FT to visualize the ulnar and median nerves in MMN, ALS and healthy controls and to identify diffusion values. Although the results are preliminary, and sample size is small, these results already show the differences in FA and AD values between MMN and healthy controls. A possible explanation is the immune myelin degeneration of the peripheral nerves in MMN patients which is not present in healthy controls. Although we did not find any differences between ALS and MMN and ALS and healthy controls, it could be that differences will become visible when more subjects are included. A larger sample size should indicate these potential differences with more statistical power.
This study shows that combining anatomical MRI images with DTI and diffusion may provide a diagnostic technique to identify MMN patients and to potentially distinguish MMN from ALS patients. Especially for MMN patients in which no conduction blocks can be identified with EMG, this technique can be of great value. Future results should indicate whether this technique can be used to classify patients on an individual level. In MMN patients this is highly important as it allows to start treatment in an earlier stage and minimize nerve damage.

References:

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