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ORIGINAL COMMUNICATION

MRI detects peripheral nerve and adjacent muscle pathology in non-systemic vasculitic neuropathy (NSVN)

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Abstract

Background Diagnosis and disease monitoring of non-systemic vasculitic neuropathy (NSVN) are based on electrophysiological and clinical measures. However, these methods are insensitive to detect subtle differences of axonal injury. We here assessed the utility of a multiparametric MRI protocol to quantify axonal injury and neurogenic muscle damage in NSVN.

Methods Ten NSVN patients and ten age-matched controls were investigated in this single-center prospective study. All participants were assessed by diffusion tensor imaging (DTI) of the tibial nerve and multiecho Dixon MRI of soleus and gastrocnemius muscles. These data were correlated with clinical and electrophysiological data.

Results DTI scans of the tibial nerves of patients with NSVN showed significantly lower mean fractional anisotropy (FA) values (0.32 ± 0.02) compared to healthy controls (0.42 ± 0.01). FA values of NSVN patients correlated negatively with clinical measures of pain. Multiecho Dixon MRI scans revealed significantly higher intramuscular fat fractions in the soleus muscle ($19.86 \pm 6.18\%$ vs. $5.86 \pm 0.74\%$, $p = 0.0015$) and gastrocnemius muscle ($26.09 \pm 6.21\%$ vs. $3.59 \pm 0.82\%$, $p = 0.0002$) in NSVN patients compared to healthy controls.

Conclusion Our data provide a proof of concept that MRI can render information about nerve integrity and muscle pathology in NSVN. Further studies are warranted to evaluate DTI and multiecho Dixon MRI as surrogate markers in NSVN.

Keywords Non-systemic vasculitic neuropathy · DTI · Proton-density fat fraction · Polyneuropathy · Neuromuscular disease

Introduction

Non-systemic vasculitic neuropathy (NSVN) is a rare, but important differential diagnosis of a slowly progressive axonal neuropathy. It is characterized by distally accentuated asymmetric motor and sensory deficits. To establish the diagnosis, nerve biopsy is recommended [1, 2]. NSVN is usually treated with immunosuppressant agents. According to recent guidelines, corticosteroids constitute the first-line treatment complemented with cyclophosphamide in severe forms [1]. In patients who are stable or have improved, discontinuation of the medication can be considered. To monitor the therapeutic response, close follow-up is recommended [1]. To date follow-up investigations are mainly based on physical examination and electrophysiological studies. However, electrophysiological studies often failed to show clinical progression or deterioration consistently reported by NSVN patients [3]. Since the correct

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interpretation of the clinical status has implications on the therapy regime, better non-invasive surrogate markers are needed.

MRI-neurography has been used recently to visualize structural pathologies in peripheral nerves [4–6]. This investigation can be complemented by diffusion tensor imaging (DTI), which provides information about nerve damage and regeneration processes [7, 8]. Besides, the evaluation of the proton density fat fraction (PDFF) by a multiecho gradient echo sequence, the so-called multiecho Dixon MRI, has been suggested as a promising MRI-based biomarker to quantify tissue fat content. This technique has been widely used in tissue fat analysis of liver diseases [9, 10], but also to analyze muscle affection in neuromuscular disorders [11, 12].

The aim of this study was to establish an MRI protocol to assess and quantify peripheral nerve and adjacent muscle injury in NSVN patients to improve monitoring of the disease.

Materials and methods

Study design

Ten patients (five females, five males; mean age 61.09 ± 4.61 years) with NSVN and ten age-matched healthy controls (four females, six males, mean age 56.38 ± 5.45 years) were examined. All patients were diagnosed at the Department of Neurology, University Hospital of Cologne, Cologne, Germany. Diagnosis of NSVN was established according to the guidelines of the Peripheral Nerve Society [1]. All patients underwent sural nerve biopsy. Biopsy specimen fulfilled the criteria for pathologically definite vasculitic neuropathy. Patients with clinical or laboratory signs of systemic vasculitis, concomitant neuropathic disorders or contraindications against MRI were excluded. Only participants without clinical and anamnestic signs of polyneuropathy were classified as healthy controls. The local ethics committee approved the study and all subjects provided written informed consent before admission to the study. This prospective, non-randomized, clinical, single-center study was carried out in accordance with the Declaration of Helsinki.

Clinical and electrophysiological assessment

All patients underwent a detailed clinical and electrophysiological evaluation including assessment of muscle strength (Medical Research Council sum score, MRCSS) and a structured interview on neuropathic symptoms. MRCSS summarizes the strength (0–5) of six paired muscle groups (upper arm abductors, elbow flexors, wrist extensors, hip flexors, knee extensors and dorsal foot flexors) with a maximum score of 60 points. Symptoms of neuropathic pain were characterized by the patients as: not present, mild, moderate and severe. These characteristics were assigned to a corresponding number ranging from 0 to 3.

For electrophysiological examinations, standard nerve conduction studies were performed. Distal motor latencies (DML), proximal and distal compound muscle action potential (CMAP) amplitudes, and motor nerve conduction velocity (mNCV) were measured for the right tibial or peroneal nerve. Sensory nerve action potential (SNAP) amplitudes and sensory nerve conduction velocity (sNCV) of the right sural nerve were recorded antidromically.

MRI data acquisition and analysis

An MRI protocol, recently established for the examination of the sciatic nerve [6], was adapted for the examination of the tibial nerve. MRI was performed on a 3-T whole-body MR system (Ingenia, Philips Healthcare, Best, The Netherlands). Subjects were examined feet first in supine position. A 16-channel knee coil (dStream T/R Knee 16ch Coil, Philips Healthcare, Best, The Netherlands) was used for signal transmission and reception. In contrast to previous studies, the knee was positioned centrally in the coil for all measurements except for the PDFF estimation. For PDFF estimation of the intramuscular fat of the lower leg muscles using multiecho Dixon sequence, the individuals' right lower legs were placed deep into the coil with the center of the coil positioned 5–10 cm caudally of the lower pole of the patella. For both measurement positions cushion pads were used to adjust the height of the patient's back to the lower edge of the coil and the distal parts of the legs were fixed with cushions.

To detect the tibial nerve in all planes a high-resolution three-dimensional T2-weighted turbo spin echo (3D T2 TSE) sequence with fat and vessel signal suppression was used. The following parameters were used: TR = 2000, TE = 273, matrix size $216 \times 143 \times 143$, resolution $1.25 \times 1.25 \times 0.7$ mm^3, scan duration 2:30 min.

An anatomical T2-weighted mDixon TSE (2D T2 TSE) and the DTI scan were then acquired in the transversal plane oriented perpendicular to the tibial nerve. The parameters of the high-resolution 2D T2 TSE sequence were: TR = 2500 ms, TE = 60 ms, matrix size 640×468, 30 slices with 4 mm slice thickness and no interslice gap, resolution $0.3 \times 0.4 \times 4$ mm^3, scan duration 5 min.

DTI

The single-shot echo planar imaging-based DTI sequence was planned similar to the 2D T2 TSE with the following parameters: TR = 6500 ms, TE = 62 ms, matrix size 128×130, 20 slices with 4 mm slice thickness and no

interslice gap, resolution 1.5 × 1.5 × 4 mm3, *b* values of 0 s/mm^2 and 800 s/mm^2, each in 20 directions, SENSE factor of 2, scan duration 9:00 min.

PDFF

A transversally acquired six-echo multiecho gradient echo sequence (mDixon Quant, Philips Healthcare, Best, The Netherlands) was used for intramuscular fat quantification. The center of the stack was placed 5–10 cm caudally of the lower part of the patella, including parts of the soleus and gastrocnemius muscles. The following parameters were used: TR = 10 ms, six echoes (TE1 = 1.45 ms, ΔTE = 1.1 ms), matrix 108 × 107 × 4mm^3, voxel size 1.8 × 1.8 × 4 mm, 20 slices, flip angle 3° (to minimize T1 bias effects), acquisition time of 1:05 min. The PDFF quantification was done using a complex-based water–fat separation with a signal model considering the multipeak fat spectrum and modeling a single T2* decay.

Data analysis

An experienced staff radiologist (T.L.) and a fellow radiologist (K.S.) independently analyzed the MR images.

All postprocessing was done using IntelliSpace Portal (IntelliSpace Portal 9.0, Philips Healthcare, Amsterdam, The Netherlands). For analysis of DTI data six freehand ROIs in six neighboring slices of each examination were drawn in the color-coded fractional anisotropy (FA) images in correlation with the anatomical information of the *b* = 0 and the 2D T2 TSE images. The average FA values of the ROIs were re-averaged to obtain the final FA value. For visualization fiber tracking of the tibial nerve was done.

To determine the average intramuscular fat fraction a freehand, subtotal ROI was drawn in the soleus muscle and each head of the gastrocnemius muscle in the PDFF maps of the multiecho Dixon scans. ROIs were drawn within 2 mm within the muscle boundaries as visually observed on a representative layer of the PDFF maps. For the gastrocnemius heads the differing area sizes (A_i) of the individual ROIs [ROI_i with individual fat fractions (FF_i)] were taken into account using the formula FF_mean_over_ROIs = sum (A_i × FF_i)/sum (A_i), where sum is the summation over both ROIs.

Statistical analysis

Statistical analysis was performed using the Mann–Whitney *U* test for group comparison. Nonparametric Spearman correlation tests (graph pad prism) were used for assessing correlations. $p < 0.05$ was considered statistically significant. Statistical analysis of interrater agreement was performed in Medcalc (V.18.11, Ostend, Belgium) calculating intraclass correlation coefficients (ICCs) and interrater agreement.

Results

Clinical and electrophysiological characteristics

Clinical and electrophysiological characteristics of the participants are listed in Tables 1 and 2. Patients suffered either from symmetrical affection of the lower extremities or multifocal affection with predominance of the right lower limb. Eight from ten patients with NSVN were treated with cyclophosphamide, one patient received corticosteroids, and one did not receive any immunosuppressive therapy. Overall, NSVN patients showed severe axonal motor and sensory affection, indicated by absent CMAPs and SNAPs in the majority of patients. Pain was moderate or severe in most patients and did not correlate with electrophysiological measures. Controls showed no clinical or anamnestic signs of small or large nerve fiber affection.

DTI

DTI scans of the tibial nerves of patients with NSVN showed lower mean FA values (0.32 ± 0.02) compared to healthy controls (0.42 ± 0.01, $p = 0.0007$, Fig. 1). ICC and interrater agreement for DTI was excellent (ICC 0.94, kappa 0.76 ± 0.05).

PDFF mapping

Multiecho Dixon scans of NSVN patients showed significantly higher intramuscular fat fractions in the soleus muscle as well as in the gastrocnemius muscle compared to healthy controls. Mean values for the soleus muscle were 19.86 ± 6.18% (NSVN) vs. 5.86 ± 0.74% (healthy controls; $p = 0.0015$) and for the gastrocnemius muscle 26.09 ± 6.21% (NSVN) vs. 3.59 ± 0.82% (healthy controls; $p = 0.0002$, Fig. 2). ICC and interrater agreement for PDFF mapping was excellent (gastrocnemius muscle: ICC 0.98, kappa 0.84 ± 0.04, soleus muscle: ICC 0.99, kappa 0.72 ± 0.07).

Table 1 Clinical characteristics

	NSVN	Controls	*p* value
Sex (female:male)	5:5	4:6	
Age (years)	61.09	56.38	0.47
Disease duration (years)	1.8	n.a.	n.a.
Treatment (cyclophosphamide)	8/10	n.a.	n.a.

Table 2 Electrophysiological characteristics

Patient	Tibial nerve		Peroneal nerve		Sural nerve	
	NCV (m/s)	CMAP (mV)	NCV (m/s)	CMAP (mV)	NCV (m/s)	SNAP (µV)
1	26	0.7	30	0.4	n.a.	n.a.
2	absent	absent	absent	absent	absent	absent
3	21	0.7	37	0.5	n.a.	n.a.
4	absent	absent	absent	absent	37	0.1
5	28	0.1	27	0.2	absent	absent
6	absent	absent	n.a.	n.a.	absent	absent
7	45	10	49	1.9	absent	absent
8	absent	absent	n.a.	n.a.	absent	absent
9	41	0.1	absent	absent	n.a.	n.a.
10	10	0.1	30	2.5	19	8

n.a. not applicable, *NCV* nerve conduction velocity, *CMAP* compound muscle action potential, *SNAP* sensory nerve action potential

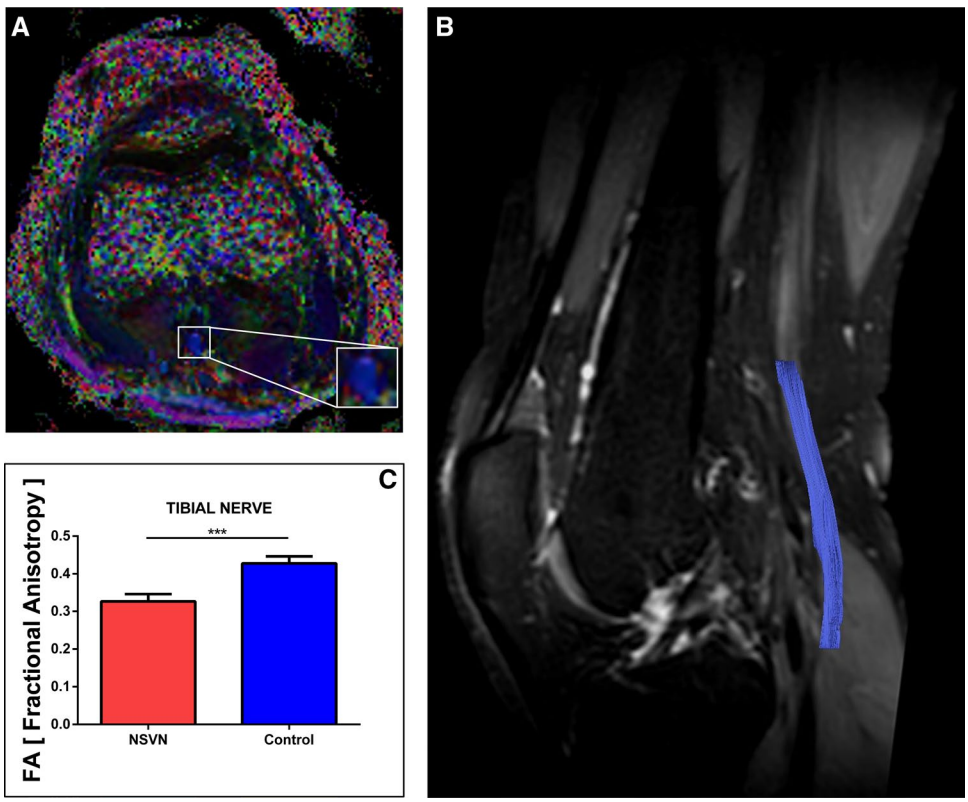

Fig. 1 **a** Color-coded FA map at the patella level of a healthy control, insert: enlargement of the proximal tibial nerve. The nerve is shown in blue as color encodings for head-feed direction. **b** Deterministic fiber tracking of the tibial nerve projected onto a sagittal reconstruction of the 3D T2 TSE sequence. **c** In NSVN patients the mean FA was significantly lower than in healthy controls

Clinical and electrophysiological correlations

MRI parameters were correlated to clinical and electrophysiological measurements. FA values of the NSVN patients correlated negatively with clinical measures of pain. Lower FA values were associated with more pain ($r = -0.57$, $p = 0.02$, Fig. 3). No significant correlation was detected between MRI and electrophysiological parameters (NCVs, CMAPs, DMLs, SNAPs, data not shown).

Discussion

We here demonstrate for the first time that in NSVN, peripheral nerve damage and muscle changes can be reliably detected by a multiparametric MRI protocol that includes DTI and PDFF.

We found significantly reduced FA values in the tibial nerve of NSVN patients, compared to healthy controls. Preclinical studies in rats and mice that included

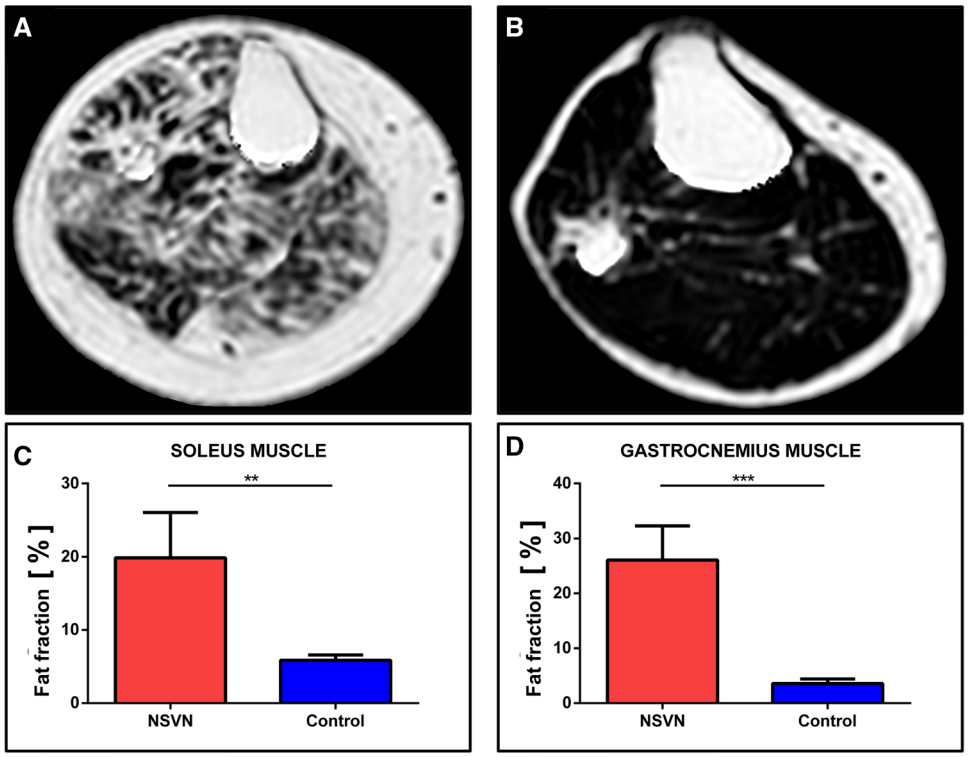

Fig. 2 Fat quantification of the soleus and gastrocnemius muscles. **a, b** PDFF maps of proximal lower leg muscles of a NSVN patient and a healthy control, with surrounding artifacts removed by post-processing. In **a** a significantly higher intramuscular fat fraction, which is associated with neurogenic muscular atrophy, is shown as a signal increase compared to the healthy control (**b**). **c, d** Average intramuscular fat fraction in soleus and gastrocnemius muscles in NSVN and controls. The mean intramuscular fat fraction is significantly higher in NSVN patients than in healthy controls

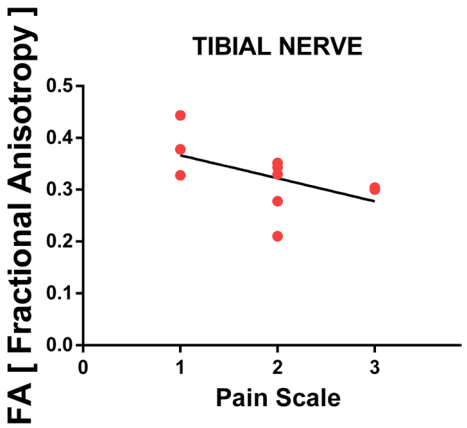

Fig. 3 Severity of neuropathic pain in NSVN patients was attributed to a corresponding number from 0 to 3 (absent/mild/moderate/severe). These numeric score correlated negatively with fractional anisotropy (FA) values of DTI scans

correlations between MRI data and nerve histology consistently demonstrated that the FA correlates with axonal injury [13–15]. Therefore, we conclude that the reduced FA values in the tibial nerves in our cohort most likely reflect the axonal damage in NSVN pathology [16]. FA values of tibial nerves in NSVN patients were significantly correlated with pain severity, but not with electrophysiological measures of axonal damage. The lack of correlation between CMAP amplitudes and FA values in our cohort can be explained by the overall severe affection of our patients and the small sample size. Within our cohort, the CMAPs were low or entirely absent, which may have prevented the detection of any correlation. Moreover, standard nerve conduction studies as applied here stimulate the tibial nerve either more distally or in the popliteal fossa, where the nerve is often stimulated submaximally. Further, in NSVN it is well known that nerve conduction studies do not correlate with disease severity and current treatment recommendations emphasize the importance of the patients' symptoms rather than their nerve conduction studies [1]. Thus and because of our finding that the FA correlated with the clinical symptom pain, we suggest that DTI can serve as a complementary biomarker for the diagnosis and disease severity in NSVN.

In line with our results, recent publications demonstrated also the feasibility of DTI to detect nerve damage in other neuropathic conditions such as chronic inflammatory demyelinating polyneuropathy (CIDP) [6, 17], or nerve compression syndromes [8]. Studies of the tibial nerve of CIDP patients showed significantly lower FA values compared to controls [17]. Kakuda et al. hypothesized that these results implied axonal damage, as they correlated with CMAP amplitudes but not nerve conduction velocities. Mean FA values in our cohort were even lower (0.32) compared to Kakuda's results (0.40), which may underline the predominant axonal damage of vasculitic neuropathies compared to CIDP. However, the FA values

of the control patients also differed in the two studies (0.53 vs. 0.42), so that methodical differences cannot be ruled out.

Moreover, our study proves the feasibility of PDFF to detect pathological abnormalities in peripheral muscles of NSVN patients. PDFF has been used recently as a biomarker of tissue fat concentration in neuromuscular diseases [11, 12], as well as in liver steatosis, where a close correlation to bioptic findings was observed [9].

Our results demonstrate that in NSVN distal muscles show a higher fat fraction compared to controls. These results are in line with reports on NSVN stating that this entity affects peripheral nerves and muscles [18, 19]. Our observation that PDFF values of the gastrocnemius and soleus muscle did not correlate with FA values of the tibial nerve, might be explained by the fact that a significant proportion of nerve fibers within the tibial nerve are of sensory origin and that their affection cannot cause muscle degeneration. Alternatively, these results might indicate that muscle affection is not primarily of neurogenic origin, but the consequence of vasculitic alterations of the muscles' blood perfusion. Further pathological studies of NSVN biopsies are warranted to address this issue.

In conclusion, this is the first study to show the feasibility of a multiparametric MRI protocol including DTI and PDFF in NSVN. Our data demonstrate affection of peripheral nerves and adjacent muscles in NSVN. The results correlated with clinical symptoms indicating its potential as a surrogate marker. To confirm our data and to establish this technique in clinical settings larger trials are warranted.

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Author contributions CS: study concept, conducting the study, data interpretation, drafting the manuscript. AS: study concept, conducting the study, analysis of data, drafting the manuscript. KW: study concept, technical assistance. KS: analysis of data. DM: study concept, drafting the manuscript for content. GRF: study concept, drafting the manuscript for content. TH: study concept. HCL: study concept, drafting the manuscript for content. TL: study concept, data analysis, drafting the manuscript.

Compliance with ethical standards

Conflicts of interest KW is an employee of Philips Healthcare Germany since 10/2014. He reports personal fees from Philips Healthcare Germany, during the conduct of the study and personal fees from Philips Healthcare Germany, outside the submitted work. The other authors state that there is no conflict of interest.

Ethical standards All procedures involving human participants were in accordance with the ethical standards of the institutional research committee and the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Informed consent Informed consent was obtained from all the individual participants included in the study.

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